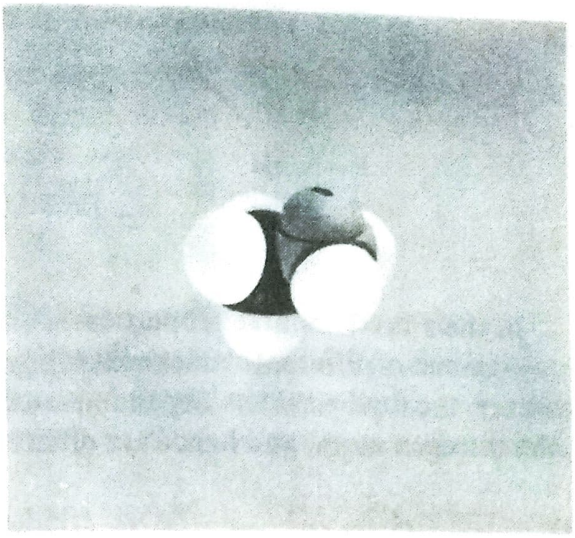
22



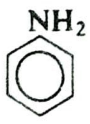
Amines I. Preparation and Physical Properties

22.1 Structure

Nearly all the organic compounds that we have studied so far are bases, although very weak ones. Much of the chemistry of alcohols, ethers, esters, and even of alkenes and aromatic hydrocarbons is understandable in terms of the basicity of these compounds.

Of the organic compounds that show appreciable basicity (for example, those strong enough to turn litmus blue), by far the most important are the **amines**. An amine has the general formula RNH_2, R_2NH, or R_3N, where R is any alkyl or aryl group. For example:

CH_3NH_2	$(CH_3)_2NH$	$(CH_3)_3N$	$H_2NCH_2CH_2NH_2$
Methylamine	Dimethylamine	Trimethylamine	Ethylenediamine
(1°)	(2°)	(3°)	(1°)



Aniline
(1°)

N-Methylaniline
(2°)

N,*N*-Dimethylaniline
(3°)

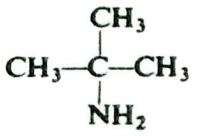
22.2 Classification

Amines are classified as **primary**, **secondary**, or **tertiary**, according to the number of groups attached to the nitrogen atom.

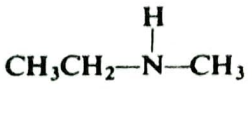
In their fundamental properties—*basicity* and the accompanying *nucleophilicity*—amines of different classes are very much the same. In many of their reactions, however, the final products depend upon the number of hydrogen atoms attached to the nitrogen atom, and hence are different for amines of different classes.

22.3 Nomenclature

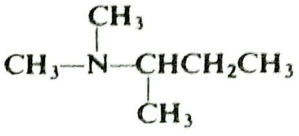
Aliphatic amines are named by naming the alkyl group or groups attached to nitrogen, and following these by the word *-amine*. More complicated ones are often named by prefixing *amino-* (or *N-methylamino-*, *N,N-diethylamino-*, etc.) to the name of the parent chain. For example:



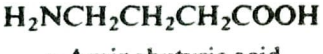
tert-Butylamine
(1°)



Ethylmethylamine
(2°)

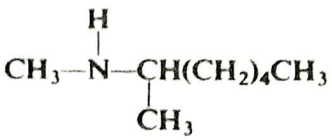


sec-Butyldimethylamine
(3°)



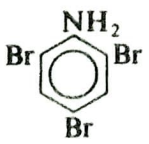
γ-Aminobutyric acid
(1°)

2-Aminoethanol
(Ethanolamine)
(1°)

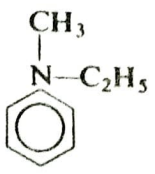


2-(*N*-Methylamino)heptane
(2°)

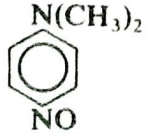
Aromatic amines—those in which nitrogen is attached directly to an aromatic ring—are generally named as derivatives of the simplest aromatic amine, **aniline**. An aminotoluene is given the special name of *toluidine*. For example:



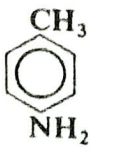
2,4,6-Tribromoaniline
(1°)



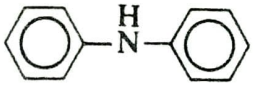
N-Ethyl-*N*-methylaniline
(3°)



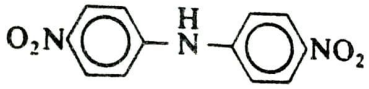
p-Nitroso-*N*,*N*-dimethylaniline
(3°)



p-Toluidine
(1°)



Diphenylamine
(2°)



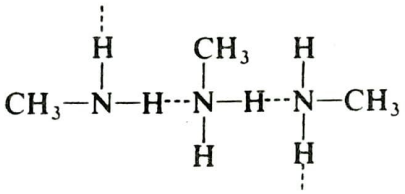
4,4′-Dinitrodiphenylamine
(2°)

Salts of amines are generally named by replacing *-amine* by *-ammonium* (or *-aniline* by *-anilinium*), and adding the name of the anion (*chloride*, *nitrate*, *sulfate*, etc.). For example:

$(C_2H_5NH_3^+)_2SO_4^{2-}$	$(CH_3)_3NH^+NO_3^-$	$C_6H_5NH_3^+Cl^-$
Ethylammonium sulfate	Trimethylammonium nitrate	Anilinium chloride

22.4 Physical properties of amines

Like ammonia, amines are polar compounds and, except for tertiary amines, can form intermolecular hydrogen bonds. Amines have higher boiling points than



non-polar compounds of the same molecular weight, but lower boiling points than alcohols or carboxylic acids.

Amines of all three classes are capable of forming hydrogen bonds with water. As a result, smaller amines are quite soluble in water, with borderline solubility being reached at about six carbon atoms. Amines are soluble in less polar solvents like ether, alcohol, benzene, etc. The methylamines and ethylamines smell very much like ammonia; the higher alkylamines have decidedly "fishy" odors.

Aromatic amines are generally very toxic; they are readily absorbed through the skin, often with fatal results.

Aromatic amines are very easily oxidized by air, and although most are colorless when pure, they are often encountered discolored by oxidation products.

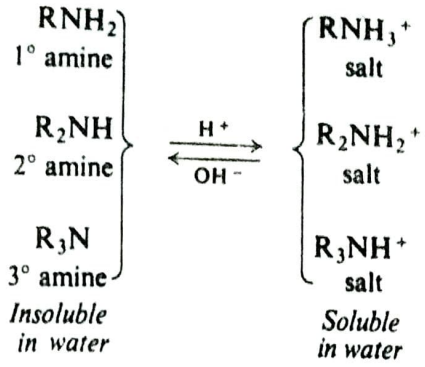
22.5 Salts of amines

Aliphatic amines are about as basic as ammonia; aromatic amines are considerably less basic. Although amines are much weaker bases than hydroxide ion or ethoxide ion, they are much stronger bases than alcohols, ethers, esters, etc.; they are much stronger bases than water. Aqueous mineral acids or carboxylic acids readily convert amines into their salts; aqueous hydroxide ion readily converts the salts back into the free amines. As with the carboxylic acids, we can do little with amines without encountering this conversion into and from their salts; it is therefore worthwhile to look at the properties of these salts.

In Sec. 19.4 we contrasted physical properties of carboxylic acids with those of their salts; amines and their salts show the same contrast. Amine salts are typical ionic compounds. They are non-volatile solids, and when heated generally decompose before the high temperature required for melting is reached. The halides, nitrates, and sulfates are soluble in water but are insoluble in non-polar solvents.

Table 22.1 AMINES

Name	M.p., °C	B.p., °C	Solubility, g/100 g H_2O	K_b
Methylamine	−92	−7.5	v.sol.	4.5×10^{-4}
Dimethylamine	−96	7.5	v.sol.	5.4×10^{-4}
Trimethylamine	−117	3	91	0.6×10^{-4}
Ethylamine	−80	17	∞	5.1×10^{-4}
Diethylamine	−39	55	v.sol.	10.0×10^{-4}
Triethylamine	−115	89	14	5.6×10^{-4}
n-Propylamine	−83	49	∞	4.1×10^{-4}
Di-*n*-propylamine	−63	110	s.sol.	10×10^{-4}
Tri-*n*-propylamine	−93	157	s.sol.	4.5×10^{-4}
Isopropylamine	−101	34	∞	4×10^{-4}
n-Butylamine	−50	78	v.sol.	4.8×10^{-4}
Isobutylamine	−85	68	∞	3×10^{-4}
sec-Butylamine	−104	63	∞	4×10^{-4}
tert-Butylamine	−67	46	∞	5×10^{-4}
Cyclohexylamine	−18	134	s.sol.	5×10^{-4}
Benzylamine	10	185	∞	0.2×10^{-4}
α-Phenylethylamine	33	187	4.2	1.2×10^{-4}
β-Phenylethylamine		195	s.	1.5×10^{-4}
Ethylenediamine	8	117	s.	0.85×10^{-4}
Tetramethylenediamine $[H_2N(CH_2)_4NH_2]$	27	158	v.sol.	
Hexamethylenediamine	39	196	v.sol.	5×10^{-4}
Tetramethylammonium hydroxide	63	135*d*	220	strong base
Aniline	−6	184	3.7	4.2×10^{-10}
Methylaniline	−57	196	v.sl.sol.	7.1×10^{-10}
Dimethylaniline	3	194	1.4	11.7×10^{-10}
Diphenylamine	53	302	i.	0.0006×10^{-10}
Triphenylamine	127	365	i.	
o-Toluidine	−28	200	1.7	2.6×10^{-10}
m-Toluidine	−30	203	s.sol.	5×10^{-10}
p-Toluidine	44	200	0.7	12×10^{-10}
o-Anisidine (*o*-$CH_3OC_6H_4NH_2$)	5	225	s.sol.	3×10^{-10}
m-Anisidine		251	s.sol.	2×10^{-10}
p-Anisidine	57	244	v.sl.sol.	20×10^{-10}
o-Chloroaniline	−2	209	i.	0.05×10^{-10}
m-Chloroaniline	−10	236		0.3×10^{-10}
p-Chloroaniline	70	232		1×10^{-10}
o-Bromoaniline	32	229	s.sol.	0.03×10^{-10}
m-Bromoaniline	19	251	v.sl.sol.	0.4×10^{-10}
p-Bromoaniline	66	*d*	i.	0.7×10^{-10}
o-Nitroaniline	71	284	0.1	0.00006×10^{-10}
m-Nitroaniline	114	307*d*	0.1	0.029×10^{-10}
p-Nitroaniline	148	332	0.05	0.001×10^{-10}
2,4-Dinitroaniline	187		s.sol.	
2,4,6-Trinitroaniline (picramide)	188		0.1	
o-Phenylenediamine [*o*-$C_6H_4(NH_2)_2$]	104	252	3	3×10^{-10}
m-Phenylenediamine	63	287	25	10×10^{-10}
p-Phenylenediamine	142	267	3.8	140×10^{-10}
Benzidine	127	401	0.05	9×10^{-10}
p-Aminobenzoic acid	187		0.3	0.023×10^{-10}
Sulfanilic acid	288*d*		1	17×10^{-10}
Sulfanilamide	163		0.4	



The difference in solubility behavior between amines and their salts can be used both to detect amines and to separate them from non-basic compounds. A water-insoluble organic compound that dissolves in cold, dilute aqueous hydrochloric acid must be appreciably basic, which means almost certainly that it is an amine. An amine can be separated from non-basic compounds by its solubility in acid; once separated, the amine can be regenerated by making the aqueous solution alkaline. (See Sec. 19.4 for a comparable situation for carboxylic acids.)

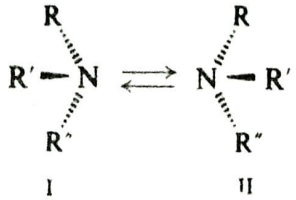
Problem 22.1 Describe exactly how you would go about separating a mixture of the three water-insoluble liquids, aniline (b.p. 184 °C), *n*-butylbenzene (b.p. 183 °C), and *n*-valeric acid (b.p. 187 °C), recovering each compound pure and in essentially quantitative yield. Do the same for a mixture of the three water-insoluble solids, *p*-toluidine, *o*-bromobenzoic acid, and *p*-nitroanisole.

22.6 Stereochemistry of nitrogen

So far in our study of organic chemistry, we have devoted considerable time to the spatial arrangement of atoms and groups attached to carbon atoms, that is, to the stereochemistry of carbon. Now let us look briefly at the stereochemistry of nitrogen.

Amines are simply ammonia in which one or more hydrogen atoms have been replaced by organic groups. Nitrogen uses sp^3 orbitals, which are directed to the corners of a tetrahedron. Three of these orbitals overlap *s* orbitals of hydrogen or carbon; the fourth contains an unshared pair of electrons (see Fig. 1.12, p. 18). Amines, then, are like ammonia, pyramidal, and with very nearly the same bond angles: 108° in trimethylamine, for example. (See Fig. 22.1 on the next page.)

From an examination of models, we can see that a molecule in which nitrogen carries three different groups is not superimposable on its mirror image; it is chiral and should exist in two enantiomeric forms (I and II) each of which—separated



from the other—might be expected to show optical activity.

But such enantiomers have not yet been isolated—for simple amines—and spectroscopic studies have shown why: the energy barrier between the two pyramidal arrangements about nitrogen is ordinarily so low that they are rapidly

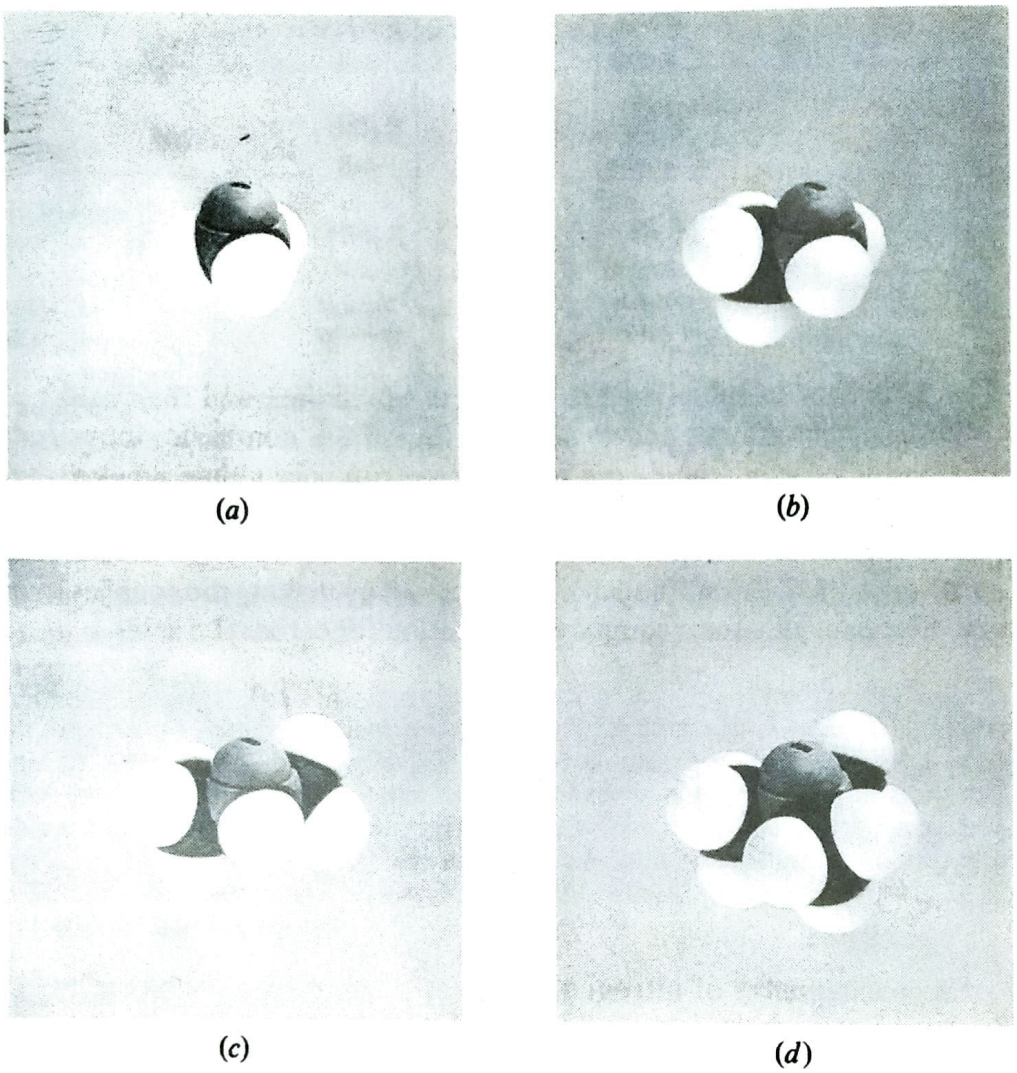
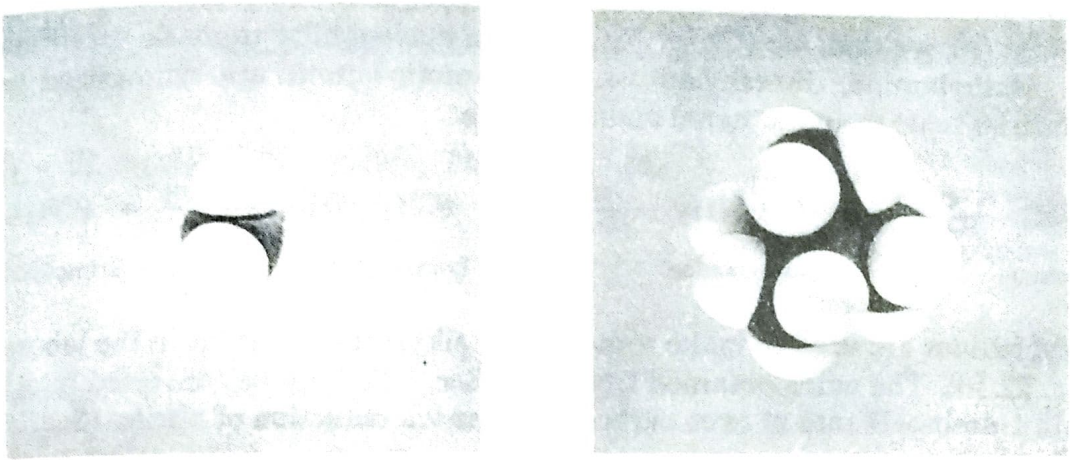


Figure 22.1 Electronic configuration and molecular shape. Models of: (*a*) ammonia, NH_3; (*b*) methylamine, CH_3NH_2; (*c*) dimethylamine, $(CH_3)_2NH$; (*d*) trimethylamine, $(CH_3)_3N$. Like ammonia, amines are pyramidal, with the unshared pair of electrons occupying the fourth sp^3 orbital of nitrogen.

interconverted. Just as rapid rotation about carbon–carbon single bonds prevents isolation of conformational enantiomers (Sec. 4.20), so rapid *inversion* about nitrogen prevents isolation of enantiomers like I and II. Evidently, an unshared pair of electrons of nitrogen cannot ordinarily serve as a fourth group to maintain configuration.

Next, let us consider the quaternary ammonium salts, compounds in which four alkyl groups are attached to nitrogen. Here all four sp^3 orbitals are used to form bonds, and quaternary nitrogen is tetrahedral. (See, for example, Fig. 22.2.) Quaternary ammonium salts in which nitrogen holds four different groups have been found to exist as *configurational* enantiomers, capable of showing optical activity: methylallylphenylbenzylammonium iodide, for example.

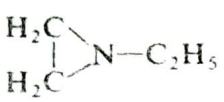
Problem 22.2 Racemization in certain free-radical and carbocation reactions has been attributed (Secs. 4.28 and 5.18) to loss of configuration in a flat intermediate. Account for the fact that the formation of alkyl carbanions, $R:^-$—which are believed to be *pyramidal*—can also lead to racemization.



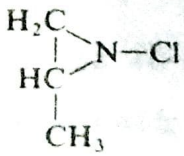
(*a*) (*b*)

Figure 22.2 Electronic configuration and molecular shape. Models of: (*a*) ammonium ion, NH_4^+; (*b*) tetramethylammonium ion, $(CH_3)_4N^+$. Like the ammonium ion, quaternary ammonium ions are tetrahedral, with nitrogen using four sp^3 orbitals.

Problem 22.3 At room temperature, the NMR spectrum of 1-ethylaziridine (III) shows the triplet–quartet of an ethyl group, and two other signals of equal peak area. When the temperature is raised to 120 °C, the latter two signals merge into a single signal. How do you interpret these observations?



III



IV

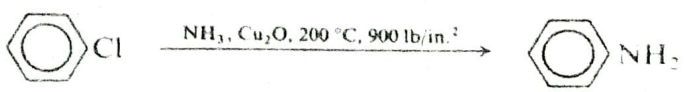
Problem 22.4 Account for the following, drawing all pertinent stereochemical formulas. (a) 1-Chloro-2-methylaziridine (IV, above) was prepared in two isomeric forms separable at 25 °C by ordinary gas chromatography. (b) The reaction of the *imine* $(C_6H_5)_2C{=}NCH_3$ with (*R*)-(+)-2-phenylperoxypropionic acid gave a product, $C_{14}H_{13}ON$, with $[\alpha]+12.5°$, which showed no loss of optical activity up to (at least) 90 °C.

22.7 Industrial source

Some of the simplest and most important amines are prepared on an industrial scale by processes that are not practicable as laboratory methods.

The most important of all amines, **aniline**, is prepared in several ways: (a) reduction of nitrobenzene by the cheap reagents, iron and dilute hydrochloric acid (or by catalytic hydrogenation, Sec. 22.9); (b) treatment of chlorobenzene with

Nitrobenzene Anilinium chloride Aniline



Chlorobenzene Aniline

ammonia at high temperatures and high pressures in the presence of a catalyst. Process (b), we shall see (Chap. 26), involves nucleophilic aromatic substitution.

Methylamine, dimethylamine, and trimethylamine are synthesized on an industrial scale from methanol and ammonia:

$$NH_3 \xrightarrow[Al_2O_3,\ 450\ ^\circ C]{CH_3OH} CH_3NH_2 \xrightarrow[Al_2O_3,\ 450\ ^\circ C]{CH_3OH} (CH_3)_2NH \xrightarrow[Al_2O_3,\ 450\ ^\circ C]{CH_3OH} (CH_3)_3N$$

Ammonia — Methylamine — Dimethylamine — Trimethylamine

Alkyl halides are used to make some higher alkylamines, just as in the laboratory (Sec. 22.10). The acids obtained from fats (Sec. 33.5) can be converted into long-chain 1-aminoalkanes of even carbon number via reduction of nitriles (Sec. 22.8).

$$\underset{\text{Acid}}{R{-}COOH} \xrightarrow{NH_3,\ heat} \underset{\text{Amide}}{R{-}CONH_2} \xrightarrow{heat} \underset{\text{Nitrile}}{R{-}C{\equiv}N} \xrightarrow{H_2,\ cat.} \underset{\text{Amine}}{R{-}CH_2NH_2}$$

22.8 Preparation

Some of the many methods that are used to prepare amines in the laboratory are outlined on the following pages.

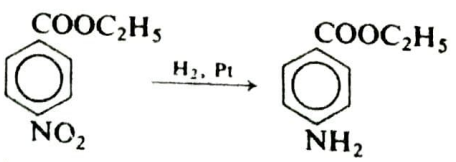
PREPARATION OF AMINES

1. Reduction of nitro compounds. Discussed in Sec. 22.9.

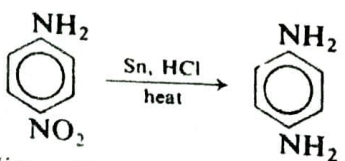
$$\underset{\text{or}}{\underset{\text{Nitro compound}}{Ar{-}NO_2 \text{ or } R{-}NO_2}} \xrightarrow{\text{metal, } H^+ \text{; or } H_2,\ \text{catalyst}} \underset{\text{or}}{\underset{1^\circ \text{ amine}}{Ar{-}NH_2 \text{ or } R{-}NH_2}}$$

Chiefly for aromatic amines

Examples:



Ethyl *p*-nitrobenzoate — Ethyl *p*-aminobenzoate



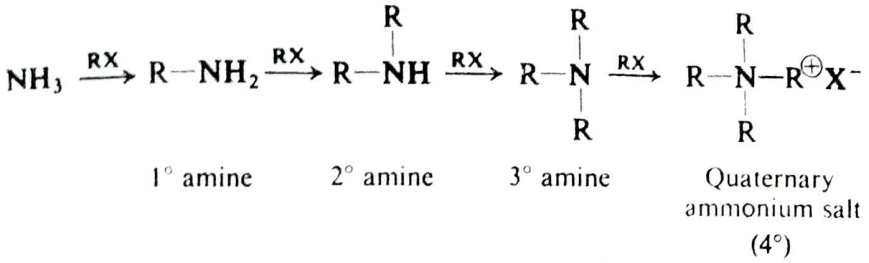
p-Nitroaniline — *p*-Phenylenediamine

$$\underset{\text{1-Nitropropane}}{CH_3CH_2CH_2NO_2} \xrightarrow{Fe,\ HCl} \underset{n\text{-Propylamine}}{CH_3CH_2CH_2NH_2}$$

CONTINUED

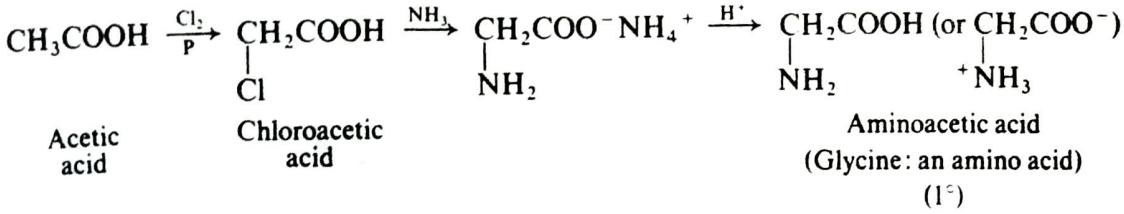
CONTINUED

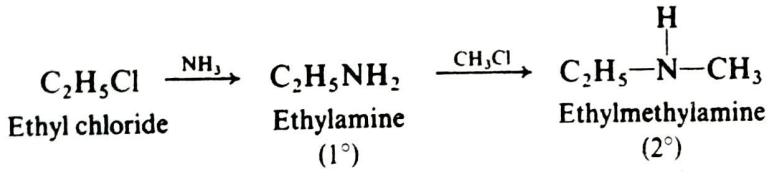
2. Reaction of halides with ammonia or amines. Discussed in Secs. 22.10 and 22.12.

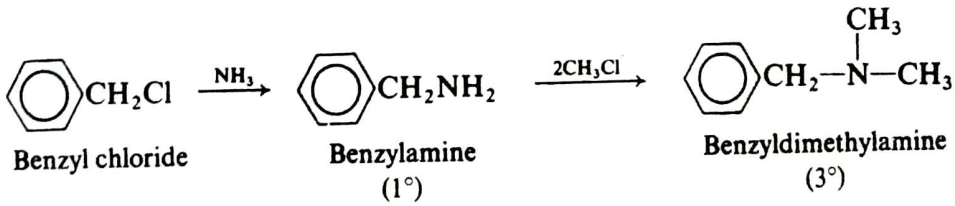


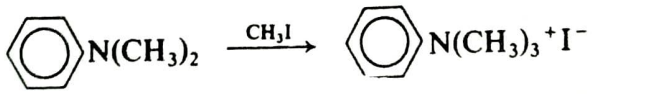
RX must be alkyl, or aryl with electron-withdrawing substituents

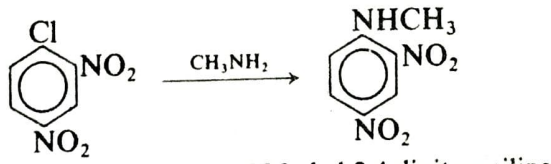
Examples:



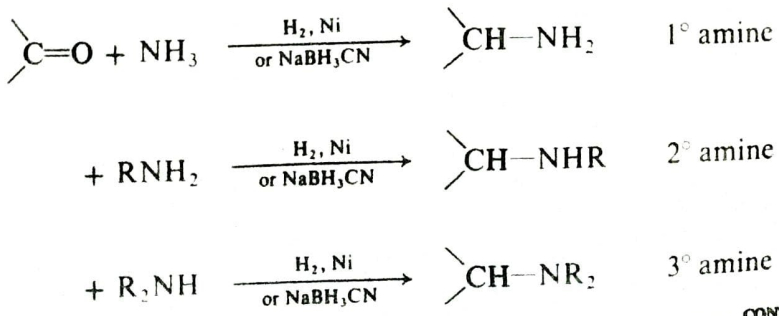








3. Reductive amination. Discussed in Sec. 22.11.



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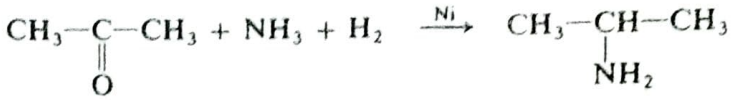
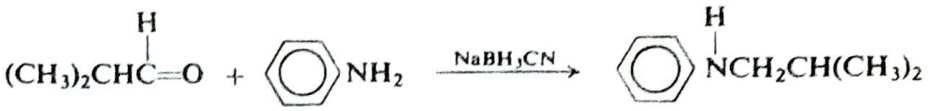
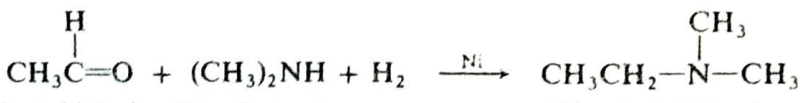
Examples:



Acetone — Isopropylamine (1°)

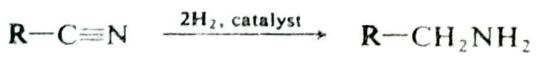


Isobutyraldehyde — Aniline (1°) — *N*-Isobutylaniline (2°)



Acetaldehyde — Dimethylamine (2°) — Dimethylethylamine (3°)

4. Reduction of nitriles. Discussed in Sec. 22.8.



Nitrile — 1° amine

Examples:

Benzyl chloride — Phenylacetonitrile (Benzyl cyanide) — *β*-Phenylethylamine (1°)

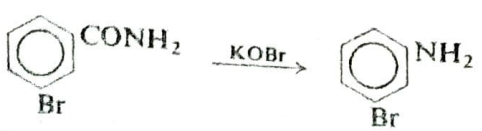
1,4-Dichlorobutane — Adiponitrile — Hexamethylenediamine (1,6-Diaminohexane) (1°)

5. Hofmann degradation of amides. Discussed in Secs. 22.13–22.15.

Amide — 1° amine

Examples:

Caproamide (Hexanamide) — *n*-Pentylamine



m-Bromobenzamide — *m*-Bromoaniline

Reduction of aromatic nitro compounds is by far the most useful method of preparing amines, since it uses readily available starting materials, and yields the most important kind of amines, *primary aromatic amines*. These amines can be converted into aromatic diazonium salts, which are among the most versatile class of organic compounds known (see Secs. 23.12–23.18). The sequence

$$\text{nitro compound} \longrightarrow \text{amine} \longrightarrow \text{diazonium salt}$$

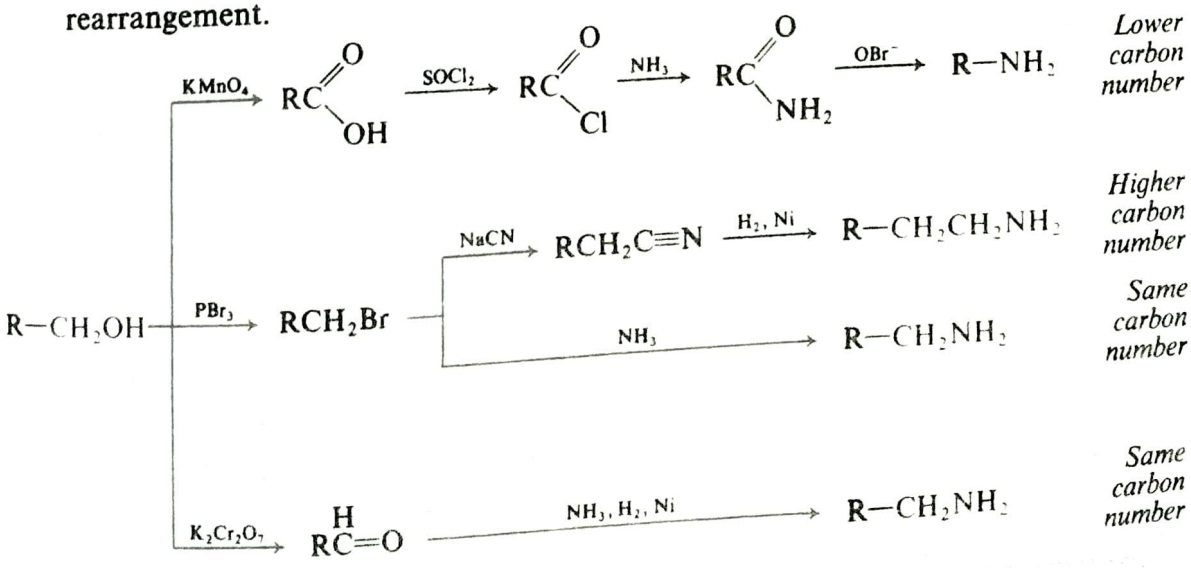
provides the best possible route to dozens of kinds of aromatic compounds.

Reduction of aliphatic nitro compounds is limited by the availability of the starting materials.

Ammonolysis of halides is usually limited to the aliphatic series, because of the generally low reactivity of aryl halides toward nucleophilic substitution. (However, see Chap. 26.) Ammonolysis has the disadvantage of yielding a mixture of different classes of amines. It is important to us as one of the most general methods of introducing the amino ($-NH_2$) group into molecules of all kinds; it can be used, for example, to convert bromo acids into amino acids. The exactly analogous reaction of halides with amines permits the preparation of every class of amine (as well as quaternary ammonium salts, $R_4N^+X^-$).

Reductive amination, the catalytic chemical reduction of aldehydes (RCHO) and ketones (R_2CO) in the presence of ammonia or an amine, accomplishes much the same purpose as the reaction of halides. It too can be used to prepare any class of amine, and has certain advantages over the halide reaction. The formation of mixtures is more readily controlled in reductive amination than in ammonolysis of halides. Reductive amination of ketones yields amines containing a *sec*-alkyl group; these amines are difficult to prepare by ammonolysis because of the tendency of *sec*-alkyl halides to undergo elimination rather than substitution.

Synthesis via **reduction of nitriles** has the special feature of *increasing the length of a carbon chain*, producing a primary amine that has one more carbon atom than the alkyl halide from which the nitrile was made. The **Hofmann degradation of amides** has the feature of *decreasing the length of a carbon chain* by one carbon atom; it is also of interest as an example of an important class of reactions involving rearrangement.

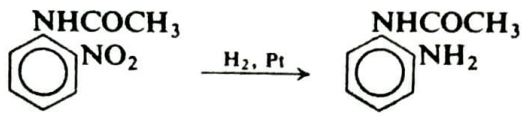


Problem 22.5 Show how *n*-pentylamine can be synthesized from available materials by the four routes just outlined.

22.9 Reduction of nitro compounds

Like many organic compounds, nitro compounds can be reduced in two general ways: (a) by catalytic hydrogenation using molecular hydrogen, or (b) by chemical reduction, usually by a metal and acid.

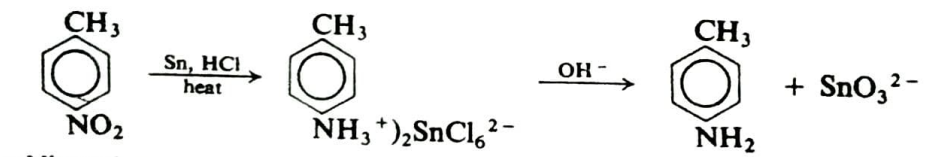
Hydrogenation of a nitro compound to an amine takes place smoothly when a solution of the nitro compound in alcohol is shaken with finely divided nickel or platinum under hydrogen gas. For example:



o-Nitroacetanilide *o*-Aminoacetanilide

This method cannot be used when the molecule also contains some other easily hydrogenated group, such as a carbon–carbon double bond.

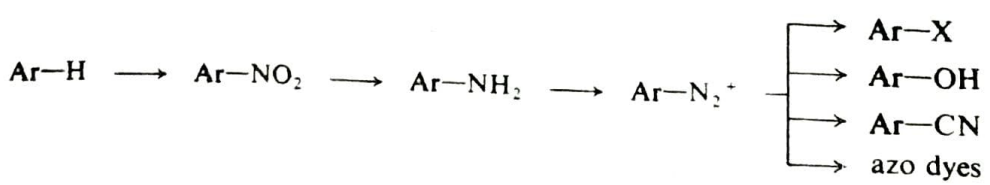
Chemical reduction in the laboratory is most often carried out by adding hydrochloric acid to a mixture of the nitro compound and a metal, usually granulated tin. In the acidic solution, the amine is obtained as its salt; the free amine is liberated by the addition of base, and is steam-distilled from the reaction mixture.



p-Nitrotoluene *p*-Toluidine

The crude amine is generally contaminated with some unreduced nitro compound, from which it can be separated by taking advantage of the basic properties of the amine; the amine is soluble in aqueous mineral acid, and the nitro compound is not.

Reduction of nitro compounds to amines is an essential step in what is probably the most important synthetic route in aromatic chemistry. Nitro compounds are readily prepared by direct nitration; when a mixture of *ortho* and *para* isomers is obtained, it can generally be separated to yield the pure isomers. The primary aromatic amines obtained by the reduction of these nitro compounds are readily converted into diazonium salts; the diazonium group, in turn, can be replaced by a large number of other groups (Sec. 23.12). In most cases this sequence is the best method of introducing these other groups into the aromatic ring. In addition, diazonium salts can be used to prepare the extremely important class of compounds, the *azo dyes*.



22.10 Ammonolysis of halides

Many organic halogen compounds are converted into amines by treatment with aqueous or alcoholic solutions of ammonia. The reaction is generally carried out either by allowing the reactants to stand together at room temperature or by

heating them under pressure. Displacement of halogen by NH_3 yields the amine salt, from which the free amine can be liberated by treatment with hydroxide ion.

$$RX + NH_3 \longrightarrow RNH_3^+X^-$$

$$RNH_3^+X^- + OH^- \longrightarrow RNH_2 + H_2O + X^-$$

Ammonolysis of halides belongs to the class of reactions that we have called nucleophilic substitution. The organic halide is attacked by the nucleophilic ammonia molecule in the same way that it is attacked by hydroxide ion, alkoxide ion, cyanide ion, acetylide ion, and water:

$$H_3N: + R{-}X \longrightarrow \left[H_3\overset{\delta+}{N}\cdots R\cdots\overset{\delta-}{X}\right] \longrightarrow H_3\overset{+}{N}{-}R + X^-$$

Like these other nucleophilic substitution reactions, ammonolysis is limited chiefly to alkyl halides or substituted alkyl halides. As with other reactions of this kind, elimination tends to compete (Sec. 8.25) with substitution: ammonia can attack hydrogen to form alkene as well as attack carbon to form amine. Ammonolysis thus gives the highest yields with primary halides (where substitution predominates) and is virtually worthless with tertiary halides (where elimination predominates).

$$CH_3CH_2CH_2CH_2Br \xrightarrow{NH_3} CH_3CH_2CH_2CH_2NH_3^+Br^- \qquad \textit{Substitution}$$

$$CH_3{-}\underset{\displaystyle Br}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}{-}CH_3 \xrightarrow{NH_3} CH_3{-}\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH_2 + NH_4Br \qquad \textit{Elimination}$$

Because of their generally low reactivity, aryl halides are converted into amines only (a) if the ring carries $-NO_2$ groups, or other strongly electron-withdrawing groups, at positions *ortho* and *para* to the halogen, or (b) if a high temperature or a strongly basic reagent is used (Chap. 26).

Some examples of the application of ammonolysis to synthesis are:

Toluene — Benzyl chloride — Benzylamine

$$CH_3CH_2COOH \xrightarrow[P]{Br_2} CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCOOH \xrightarrow{NH_3} CH_3\underset{\displaystyle NH_2}{\underset{|}{C}}HCOOH$$

Propionic acid — α-Bromopropionic acid — Alanine (α-Aminopropionic acid)

$$CH_2{=}CH_2 \xrightarrow{Cl_2} ClCH_2CH_2Cl \xrightarrow{2NH_3} H_2NCH_2CH_2NH_2$$

Ethylene — 1,2-Dichloroethane — Ethylenediamine

A serious disadvantage to the synthesis of amines by ammonolysis is the formation of more than one class of amine. The primary amine salt, formed by the

$$RX + NH_3 \longrightarrow \underset{\text{1° amine salt}}{RNH_3^+X^-}$$

initial substitution, reacts with the reagent ammonia to yield the ammonium salt and the free primary amine; the following equilibrium thus exists:

$$\underset{}{RNH_3^+} + NH_3 \rightleftharpoons \underset{\text{1° amine}}{RNH_2} + NH_4^+$$

The free primary amine, like the ammonia from which it was made, is a nucleophilic reagent; it too can attack the alkyl halide, to yield the salt of a secondary amine:

$$\underset{\text{1° amine}}{RNH_2} + RX \longrightarrow R_2NH_2^+X^- \xrightleftharpoons{NH_3} \underset{\text{2° amine}}{R_2NH}$$

The secondary amine, which is in equilibrium with its salt, can in turn attack the alkyl halide to form the salt of a tertiary amine:

$$\underset{\text{2° amine}}{R_2NH} + RX \longrightarrow R_3NH^+X^- \xrightleftharpoons{NH_3} \underset{\text{3° amine}}{R_3N}$$

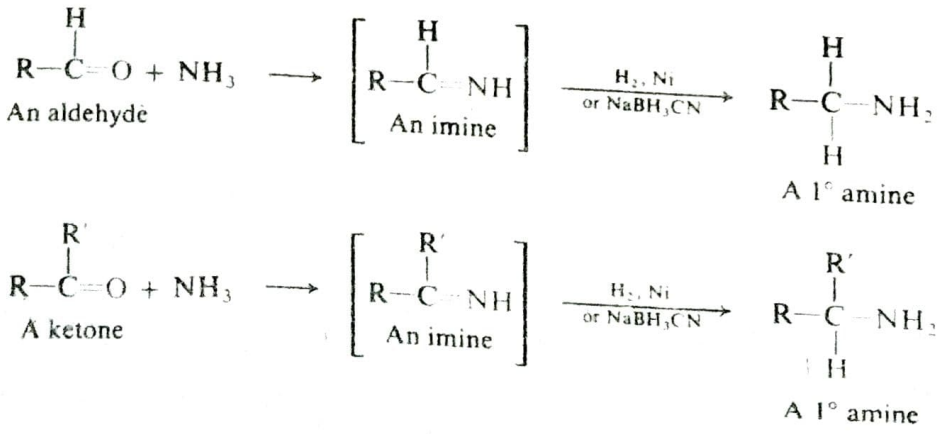
Finally, the tertiary amine can attack the alkyl halide to form a compound of the formula $R_4N^+X^-$, called a *quaternary ammonium salt* (discussed in Sec. 23.5):

$$\underset{\text{3° amine}}{R_3N} + RX \longrightarrow \underset{\substack{\text{Quaternary ammonium salt}\\(4°)}}{R_4N^+X^-}$$

The presence of a large excess of ammonia lessens the importance of these last reactions and increases the yield of primary amine; under these conditions, a molecule of alkyl halide is more likely to encounter, and be attacked by, one of the numerous ammonia molecules rather than one of the relatively few amine molecules. At best, the yield of primary amine is always cut down by the formation of the higher classes of amines. Except in the special case of methylamine, the primary amine can be separated from these by-products by distillation.

22.11 Reductive amination

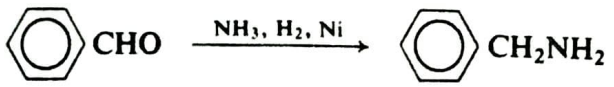
Many aldehydes (RCHO) and ketones (R_2CO) are converted into amines by **reductive amination**: reduction in the presence of ammonia. Reduction can be accomplished catalytically or by use of sodium cyanohydridoborate, $NaBH_3CN$. Reaction involves reduction of an intermediate compound (an *imine*, RCH=NH or R_2C=NH) that contains a carbon–nitrogen double bond.



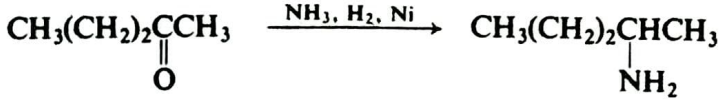
Reductive amination has been used successfully with a wide variety of aldehydes and ketones, both aliphatic and aromatic. For example:

$$CH_3(CH_2)_5CHO \xrightarrow{NH_3,\ H_2,\ Ni} CH_3(CH_2)_5CH_2NH_2$$

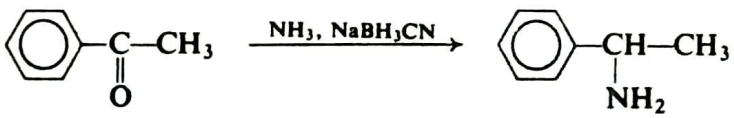
Heptaldehyde (Heptanal) → *n*-Heptylamine (1-Aminoheptane)



Benzaldehyde → Benzylamine

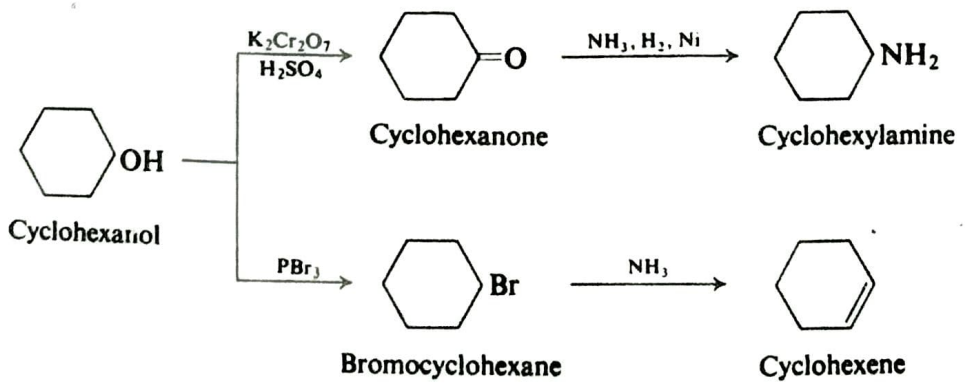


2-Pentanone (Methyl *n*-propyl ketone) → 2-Aminopentane



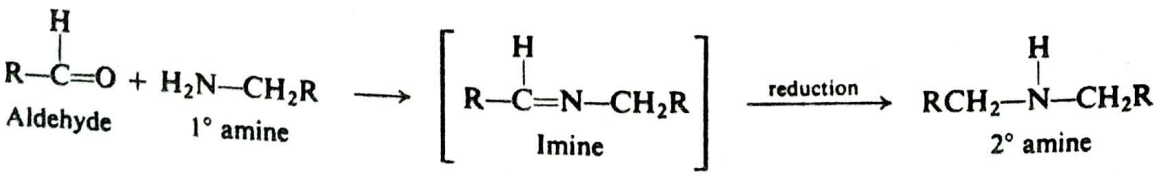
Acetophenone (Methyl phenyl ketone) → α-Phenylethylamine

Reductive amination of ketones yields amines containing a *sec*-alkyl group; such amines are difficult to obtain by ammonolysis because of the tendency for *sec*-alkyl halides to undergo elimination. For example, cyclohexanone is converted into cyclohexylamine in good yield, whereas ammonolysis of bromocyclohexane yields only cyclohexene.



Cyclohexanol → Cyclohexanone → Cyclohexylamine; Cyclohexanol → Bromocyclohexane → Cyclohexene

During reductive amination the aldehyde or ketone can react not only with ammonia but also with the primary amine that has already been formed, and thus yield a certain amount of secondary amine. The tendency for the reaction to go

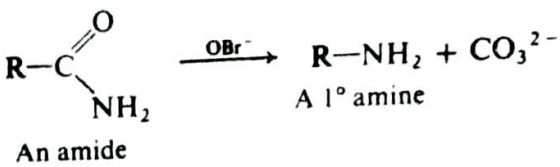


Aldehyde + 1° amine → Imine → 2° amine

beyond the desired stage can be fairly well limited by the proportions of reactants employed and is seldom a serious handicap.

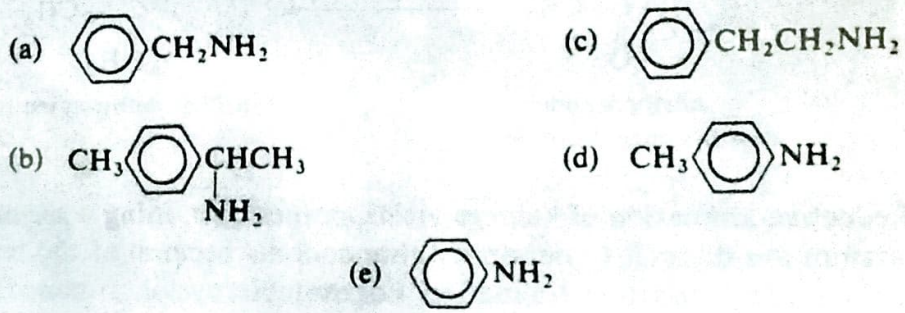
22.12 Hofmann degradation of amides

As a method of synthesis of amines, the Hofmann degradation of amides has the special feature of yielding a product containing one less carbon than the starting material. As we can see, reaction involves migration of a group from carbonyl



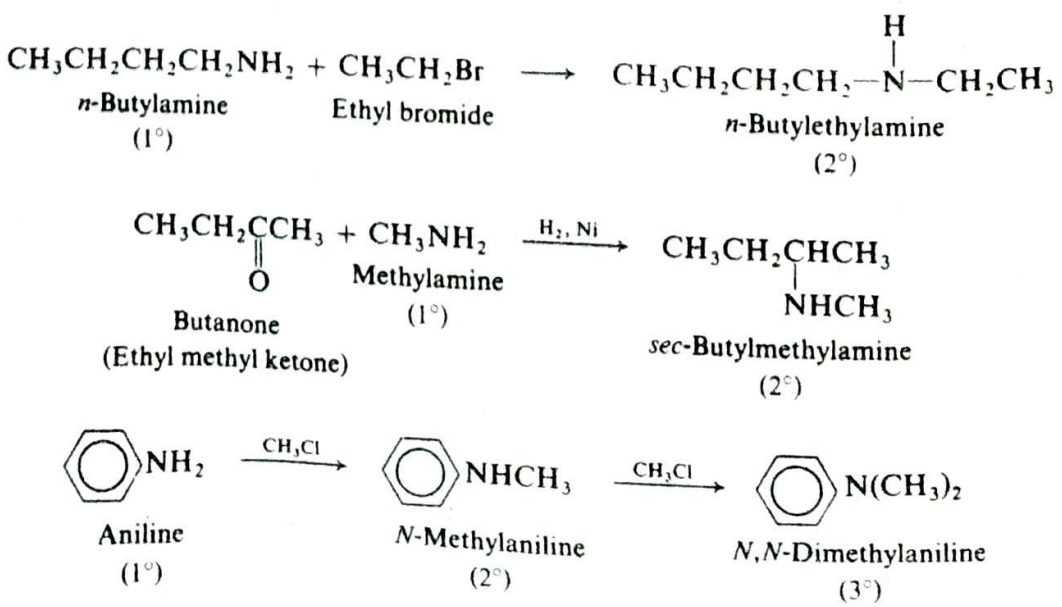
carbon to the adjacent nitrogen atom, and thus is an example of a *molecular rearrangement*. (We shall return to the Hofmann degradation in Secs. 22.15–22.17 and discuss its mechanism in detail.)

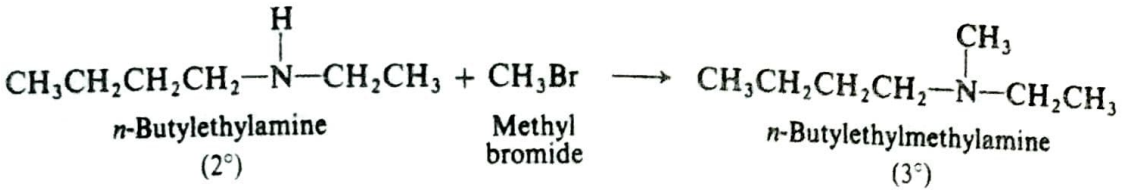
Problem 22.6 Using a different method in each case, show how the following amines could be prepared from *toluene* and any aliphatic reagents:



22.13 Synthesis of secondary and tertiary amines

So far we have been chiefly concerned with the synthesis of primary amines. Secondary and tertiary amines are prepared by adaptations of one of the processes already described: ammonolysis of halides or reductive amination. For example:





Where ammonia has been used to produce a primary amine, a primary amine can be used to produce a secondary amine, or a secondary amine can be used to produce a tertiary amine. In each of these syntheses there is a tendency for reaction to proceed beyond the first stage and to yield an amine of a higher class than the one that is wanted.

Problem 22.7 If a tertiary amine is heated with an alkyl halide and the product treated with aqueous silver oxide and filtered, the resulting solution is as strongly alkaline as a solution of sodium hydroxide. What is in the solution, and why is it so basic?

22.14 Heterocyclic amines

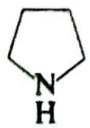
A particularly important kind of amino compound is one in which the nitrogen makes up part of a ring. Since such a ring contains more than one kind of atom—nitrogen plus the usual carbon—the compound of which it is a part is said to be *heterocyclic*. (Compare, for example, the heterocyclic oxygen compounds in Secs. 13.18–13.20.) We shall discuss heterocyclic compounds in detail in Chapter 30. But it is hard to go very far in organic chemistry without encountering heterocyclic nitrogen compounds—indeed, we have already encountered them as reagents—and so we shall look briefly at some of them here.

These heterocyclic amines can be saturated or unsaturated, aliphatic or aromatic; a nitrogen may share the ring with another nitrogen or with a hetero atom of a different kind—oxygen, say, or sulfur. For example:

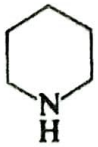
Pyrrole

Pyridine

Pyrimidine



Pyrrolidine



Piperidine

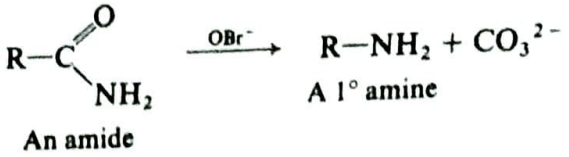
Purine

The important thing for us to realize at this point is that, part of a ring or not, nitrogen is still nitrogen. It retains its most important property, *basicity*; and this basicity, as we shall see in the next chapter, is the property that determines the chemical behavior of amines.

We have all heard of the *bases* whose sequence along the DNA molecule constitutes the genetic code. These bases are heterocyclic bases, and their basicity comes from nitrogen.

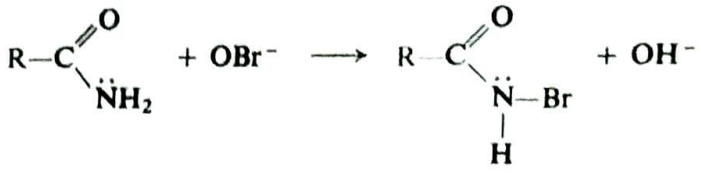
22.15 Hofmann rearrangement. Migration to electron-deficient nitrogen

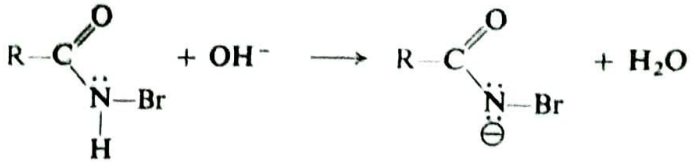
Let us return to a reaction that we encountered earlier as a method of synthesis of amines: the Hofmann degradation of amides. Whatever the mechanism of the

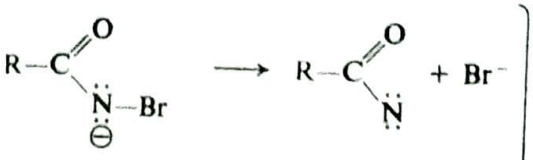


reaction, it is clear that rearrangement occurs, since the group joined to carbonyl carbon in the amide is found joined to nitrogen in the product.

The reaction is believed to proceed by the following steps:

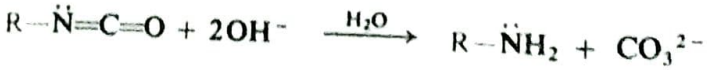
(1) 

(2) 

(3) 

(4) 

Simultaneous

(5) 

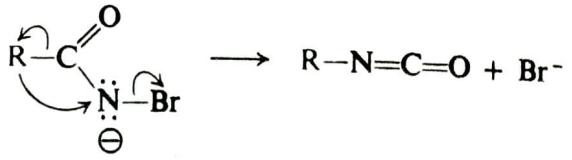
Step (1) is the halogenation of an amide. This is a known reaction, an *N*-haloamide being isolated if no base is present. Furthermore, if the *N*-haloamide isolated in this way is then treated with base, it is converted into the amine.

Step (2) is the abstraction of a hydrogen ion by hydroxide ion. This is reasonable behavior for hydroxide ion, especially since the presence of the electron-withdrawing bromine increases the acidity of the amide. Unstable salts have actually been isolated in certain of these reactions.

Step (3) involves the separation of a halide ion, which leaves behind an electron-deficient nitrogen atom.

In Step (4) the actual rearrangement occurs. Steps (3) and (4) are generally believed to occur simultaneously, the attachment of R to nitrogen helping to push out halide ion.

(3,4)



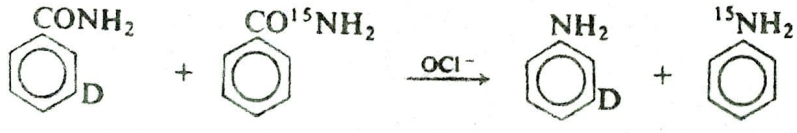
Step (5) is the hydrolysis of an isocyanate (R—N=C=O) to form an amine and carbonate ion. This is a known reaction of isocyanates. If the Hofmann degradation is carried out in the absence of water, an isocyanate can actually be isolated.

Like the rearrangement of carbocations that we have already encountered (Sec. 5.22), the Hofmann rearrangement involves a 1,2-shift. In the rearrangement of carbocations a group migrates with its electrons to an electron-deficient carbon; in the present reaction the group migrates with its electrons to an electron-deficient *nitrogen*. We consider nitrogen to be electron-deficient even though it probably loses electrons—to bromide ion—*while* migration takes place, rather than before.

The strongest support for the mechanism just outlined is the fact that many of the proposed intermediates have been isolated, and that these intermediates have been shown to yield the products of the Hofmann degradation. The mechanism is also supported by the fact that analogous mechanisms account satisfactorily for observations made on a large number of related rearrangements. Furthermore, the actual rearrangement step fits the broad pattern of 1,2-shifts to electron-deficient atoms.

In addition to evidence indicating what the various steps in the Hofmann degradation are, there is also evidence that gives us a rather intimate view of just how the rearrangement step takes place. In following sections we shall see what some of that evidence is. We shall be interested in this not just for what it tells us about the Hofmann degradation, but because it will give us an idea of the kind of thing that can be done in studying rearrangements of many kinds.

Problem 22.8 The Hofmann degradation of a mixture of *m*-deuteriobenzamide and benzamide-^{15}N gives *only* *m*-deuterioaniline and aniline-^{15}N. What does this finding show about the nature of the migration step?



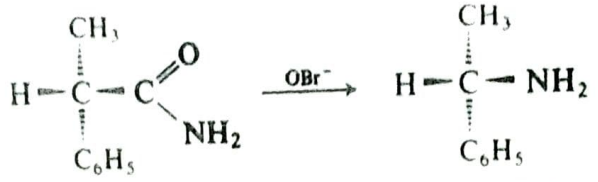
Only rearrangement products

Problem 22.9 Reaction of acid chlorides with sodium azide, NaN_3, yields *acyl azides*, $RCON_3$. When heated, these undergo the *Curtius rearrangement* to amines, RNH_2, or, in a non-hydroxylic solvent, to isocyanates, RNCO. Using the structure

for the azide, suggest a mechanism for the rearrangement. (*Hint*: Write balanced equations.)

22.16 Hofmann rearrangement. Stereochemistry at the migrating group

When optically active α-phenylpropionamide undergoes the Hofmann degradation, α-phenylethylamine of the same configuration and of essentially the same optical purity is obtained:



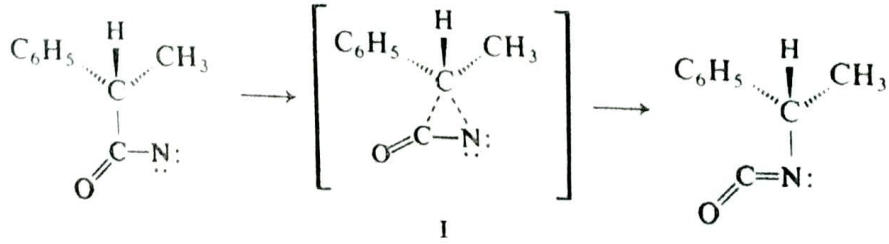
(+)-α-Phenylpropionamide (−)-α-Phenylethylamine

Retention of configuration

Rearrangement proceeds *with complete retention of configuration* about the chiral center of the migrating group.

These results tell us two things. First, nitrogen takes the same relative position on the chiral carbon that was originally occupied by the carbonyl carbon. Second, the chiral carbon does not break away from the carbonyl carbon until it has started to attach itself to nitrogen. If the group were actually to become free during its migration, we would expect considerable loss of configuration and hence a partially racemic product.

We may picture the migrating group as moving from carbon to nitrogen via a transition state, I, in which carbon is pentavalent:

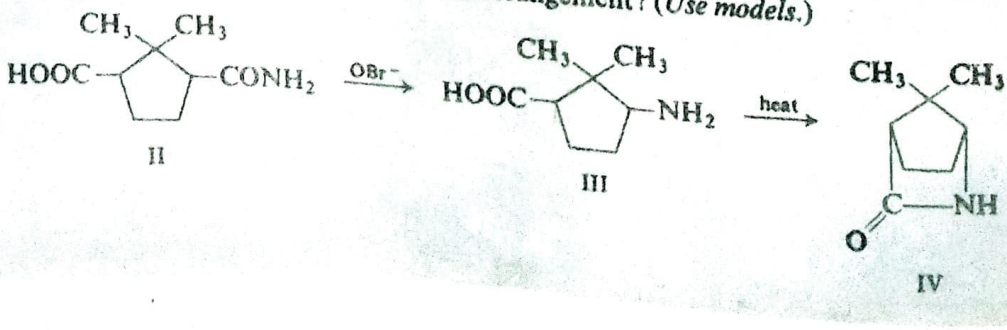


I

The migrating group *steps* from atom to atom; it does *not* jump.

There is much evidence to suggest that the stereochemistry of all 1,2-shifts has this common feature: *complete retention of configuration in the migrating group.*

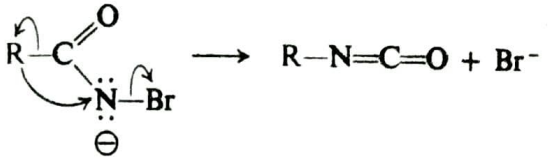
Problem 22.10 Many years before the Hofmann degradation of optically active α-phenylpropionamide was studied, the following observations were made: when the cyclopentane derivative II, in which the —COOH and —$CONH_2$ groups are *cis* to each other, was treated with hypobromite, compound III was obtained; compound III could be converted by heat into the amide IV (called a *lactam*). What do these results show about the mechanism of the arrangement? (*Use models.*)



II III IV

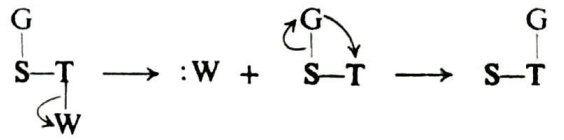
22.17 Hofmann rearrangement. Timing of the steps

We said that steps (3) and (4) of the mechanism are believed to be simultaneous, that is, that loss of bromide ion and migration occur in the same step:

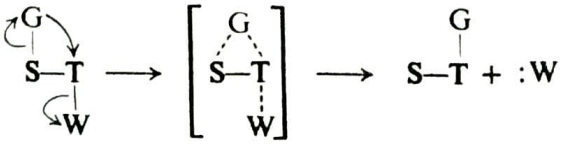


One reason for believing this is simply the anticipated difficulty of forming a highly unstable intermediate in which an electronegative element like nitrogen has only a sextet of electrons. Such a particle should be even less stable than primary carbocations, and those, we know, are seldom formed. Another reason is the effect of structure on reactivity. Let us examine this second reason.

As background, let us look more closely at the rearrangement process. An electron-deficient atom is most commonly generated by the departure of a leaving group which takes the bonding electrons with it. The migrating group is, of course, a nucleophile, and so a rearrangement of this sort amounts to *intramolecular nucleophilic substitution*. Now, as we have seen, nucleophilic substitution can be of two kinds, S_N2 and S_N1. Exactly the same possibilities exist for a rearrangement. As we have described rearrangement so far, it is S_N1-like, with the migrating group



S_N1-like migration



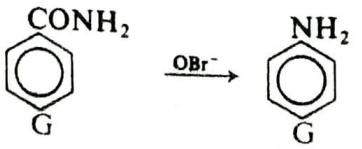
S_N2-like migration

G = migrating group
S = migration source
T = migration terminus

waiting for the departure of the leaving group before it moves. But it *could* be S_N2-like, with the neighboring group helping to push out the leaving group in a single-step reaction. This matter of *timing* of bond-breaking and bond-making is—as it is with all reactions—of major concern in the study of rearrangements.

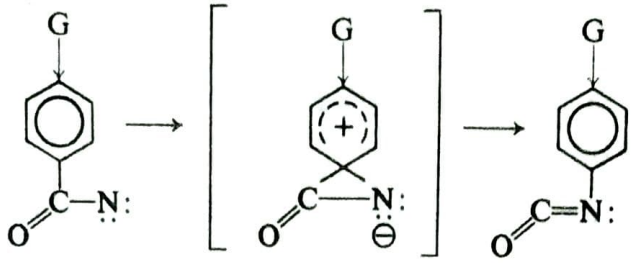
When the migrating group helps to expel the leaving group, it is said to give *anchimeric assistance* (Greek: *anchi* + *meros*, adjacent parts).

Now, to return to the Hofmann degradation. When the migrating group is aryl, the rate of the degradation is increased by the presence of electron-releasing substituents in the aromatic ring; thus substituted benzamides show the following order of reactivity:



$$-OCH_3 > -CH_3 > -H > -Cl > -NO_2$$

Now, how could electron release speed up Hofmann degradation? One way could be through its effect on the rate of migration. Migration of an alkyl group must involve a transition state containing pentavalent carbon, like I in the preceding section. Migration of an aryl group, on the other hand, takes place via a structure like V. This structure is a familiar one; from the standpoint of the migrating aryl group, rearrangement is simply electrophilic aromatic substitution, with the electron-deficient atom—nitrogen, in this case—acting as the attacking reagent. In at least some rearrangements, there is evidence that structures like V



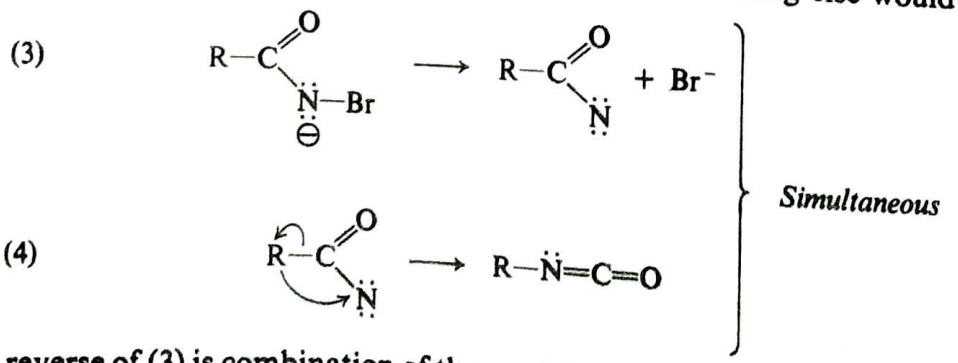
V

are actual intermediate compounds, as in the ordinary kind of electrophilic aromatic substitution (Sec. 15.14). Electron-releasing groups disperse the developing charge on the aromatic ring and thus speed up formation of V. Viewed in this way, substituents affect the rate of rearrangement—the *migratory aptitude*—of an aryl group in exactly the same way as they affect the rate of aromatic nitration, halogenation, or sulfonation. (In some cases, however, conformational effects can completely outweigh these electronic effects.)

There is another way in which electron release might be speeding up reaction: by speeding up formation of the electron-deficient species in equation (3). But the observed effect is a strong one, and more consistent with the development of the positive charge *in the ring itself*, as during rearrangement.

We should be clear about what the question is here. It is *not* whether some groups migrate faster than others—there is little doubt about that—but whether the rate of rearrangement affects the overall rate—the *measured* rate—of the Hofmann degradation.

It is likely, then, that electron-releasing substituents speed up Hofmann degradation by speeding up rearrangement. Now, under what conditions can this happen? Consider the sequence (3) and (4). Loss of bromide ion (3) could be fast and reversible, followed by slow rearrangement (4). Rearrangement would be rate-determining, as required, but in that case something else would not fit. The



reverse of (3) is combination of the particle ArCON with bromide ion; if this were taking place, so should combination of ArCON with the solvent, water—more abundant and more nucleophilic—to form the *hydroxamic acid* ArCONHOH. But hydroxamic acids are *not* formed in the Hofmann degradation.

If ArCON were indeed an intermediate, then, it would have to be undergoing rearrangement as fast as it is formed; that is, (4) would have to be fast compared with (3). But in that case, the overall rate would be independent of the rate of rearrangement, contrary to fact.

We are left with the concerted mechanism (3,4). Attachment of the migrating group helps to push out bromide ion, and overall rate *does* depend on the rate of rearrangement. As the amount of anchimeric assistance varies, so does the observed rate of reaction.

At the migrating group, we said, rearrangement amounts to electrophilic substitution. But at the electron-deficient nitrogen, rearrangement amounts to *nucleophilic* substitution: the migrating group (with its electrons) is a nucleophile, and bromide ion is the leaving group. The sequence (3) and (4) corresponds to an S_N1 mechanism; the concerted reaction (3,4) corresponds to a S_N2 mechanism. Dependence of overall rate on the nature of the nucleophile is consistent with the S_N2-like mechanism, but not with the S_N1-like mechanism.

PROBLEMS

1. Draw structures, give names, and classify as primary, secondary, or tertiary:

(a) the eight isomeric amines of formula $C_4H_{11}N$
(b) the five isomeric amines of formula C_7H_9N that contain a benzene ring

2. Give the structural formulas of the following compounds:

(a) *sec*-butylamine
(b) *o*-toluidine
(c) anilinium chloride
(d) diethylamine
(e) *p*-aminobenzoic acid
(f) benzylamine
(g) isopropylammonium benzoate
(h) *N*,*N*-dimethylaniline
(i) 2-aminoethanol
(j) *β*-phenylethylamine
(k) *N*,*N*-dimethylaminocyclohexane
(l) diphenylamine
(m) 2,4-dimethylaniline
(n) tetra-*n*-butylammonium iodide

3. Show how *n*-propylamine could be prepared from each of the following:

(a) *n*-propyl bromide
(b) *n*-propyl alcohol
(c) propionaldehyde
(d) 1-nitropropane
(e) propionitrile
(f) *n*-butyramide
(g) *n*-butyl alcohol
(h) ethyl alcohol

Which of these methods can be applied to the preparation of aniline? Of benzylamine?

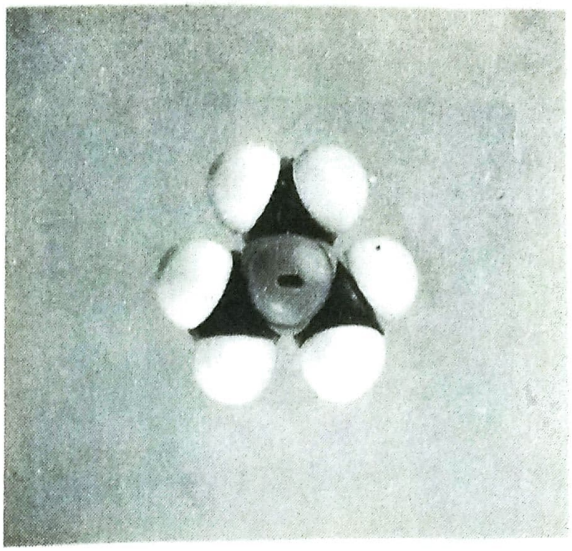
4. Outline all steps in a possible laboratory synthesis of each of the following compounds from benzene, toluene, and alcohols of four carbons or fewer using any needed inorganic reagents.

(a) isopropylamine
(b) *n*-pentylamine
(c) *p*-toluidine
(d) ethylisopropylamine
(e) α-phenylethylamine
(f) *β*-phenylethylamine
(g) *m*-chloroaniline
(h) *p*-aminobenzoic acid
(i) 3-aminoheptane
(j) *N*-ethylaniline
(k) 2,4-dinitroaniline
(l) the drug *benzedrine* (2-amino-1-phenylpropane)
(m) *p*-nitrobenzylamine
(n) 2-amino-1-phenylethanol

5. Outline all steps in a possible laboratory synthesis from palmitic acid, n-$C_{15}H_{31}COOH$, of:

(a) n-$C_{16}H_{33}NH_2$
(b) n-$C_{17}H_{35}NH_2$
(c) n-$C_{15}H_{31}NH_2$
(d) n-$C_{15}H_{31}CH(NH_2)$-n-$C_{16}H_{33}$

23



Amines II. Reactions

23.1 Reactions

Like ammonia, the three classes of amines contain nitrogen that bears an unshared pair of electrons; as a result, amines closely resemble ammonia in chemical properties (Fig. 23.1, on the next page). *The tendency of nitrogen to share this pair of electrons underlies the entire chemical behavior of amines*: their basicity, their action as nucleophiles—in both aliphatic and acyl substitution—and the unusually high reactivity of aromatic rings bearing amino or substituted amino groups.

With certain reagents the product that is actually obtained can vary, depending upon the class of the amine. Even here, we shall find, reaction takes the same basic (key word!) course at first; it is just that what finally happens depends upon how many hydrogens the nitrogen carries, that is, upon the class of the amine.

REACTIONS OF AMINES

1. **Basicity. Salt formation.** Discussed in Secs. 22.5 and 23.2–23.4.

$$RNH_2 + H^+ \rightleftharpoons RNH_3^+$$

$$R_2NH + H^+ \rightleftharpoons R_2NH_2^+$$

$$R_3N + H^+ \rightleftharpoons R_3NH^+$$

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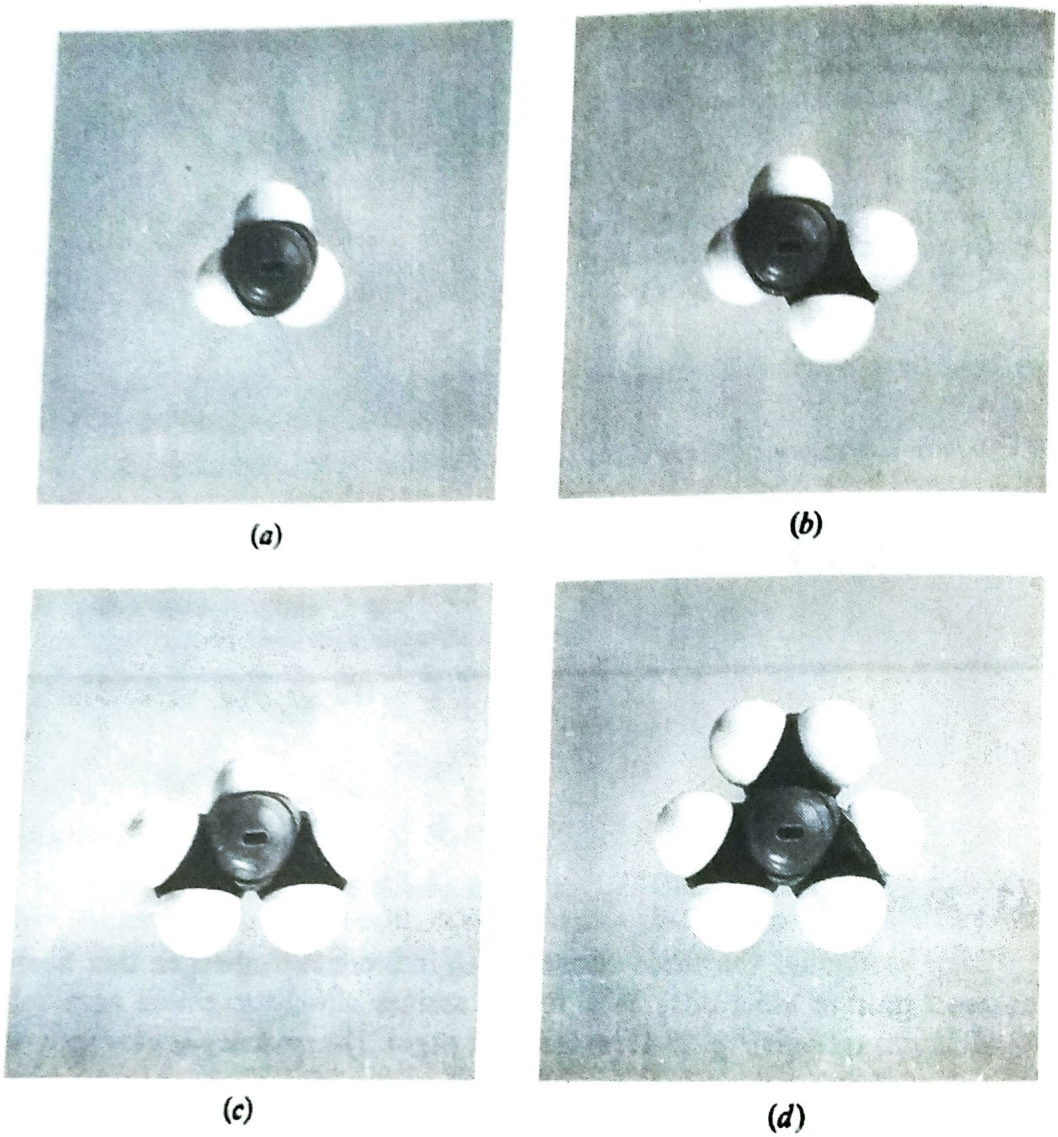

(*a*) (*b*) (*c*) (*d*)

Figure 23.1 Molecular structure and chemical reactivity. Models of: (*a*) ammonia, NH_3; (*b*) methylamine, CH_3NH_2; (*c*) dimethylamine, $(CH_3)_2NH$; (*d*) trimethylamine, $(CH_3)_3N$. The chemical behavior of amines depends upon the tendency of nitrogen to share its unshared pair of electrons, shown facing us in each model.

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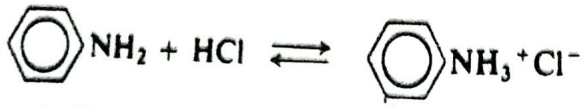
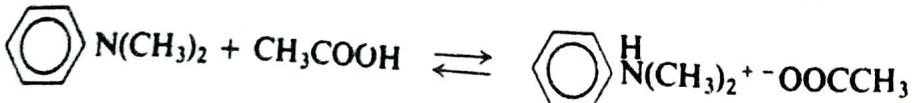
Examples:



Aniline — Anilinium chloride (Aniline hydrochloride)

$(CH_3)_2NH + HNO_3 \rightleftharpoons (CH_3)_2NH_2^+NO_3^-$

Dimethylamine — Dimethylammonium nitrate



N,*N*-Dimethylaniline — *N*,*N*-Dimethylanilinium acetate

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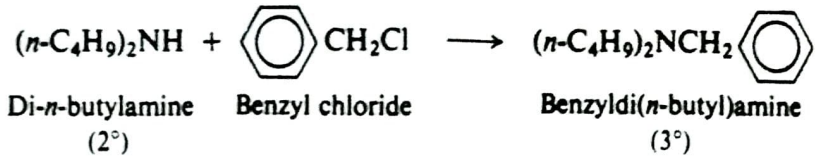
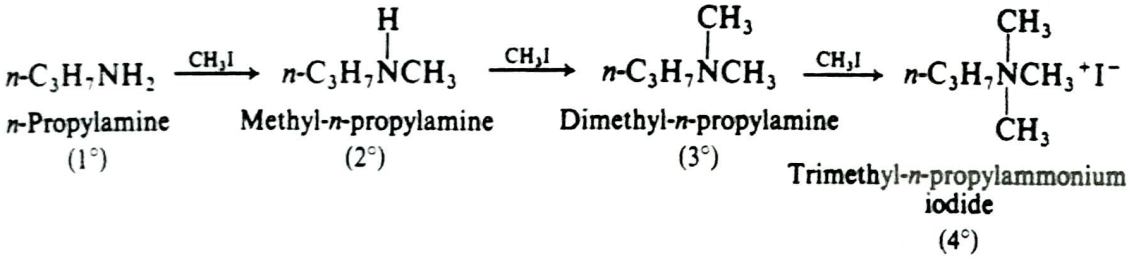
2. Alkylation. Discussed in Secs. 22.13 and 23.5.

$$RNH_2 \xrightarrow{RX} R_2NH \xrightarrow{RX} R_3N \xrightarrow{RX} R_4N^+X^-$$

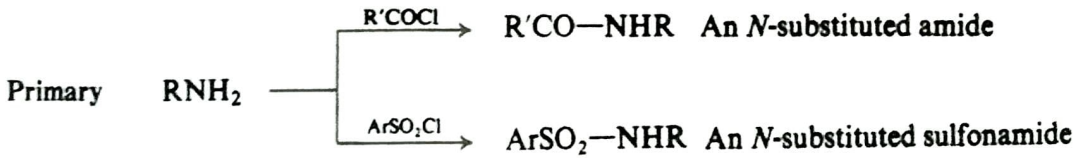
$$ArNH_2 \xrightarrow{RX} ArNHR \xrightarrow{RX} ArNR_2 \xrightarrow{RX} ArNR_3^+X^-$$

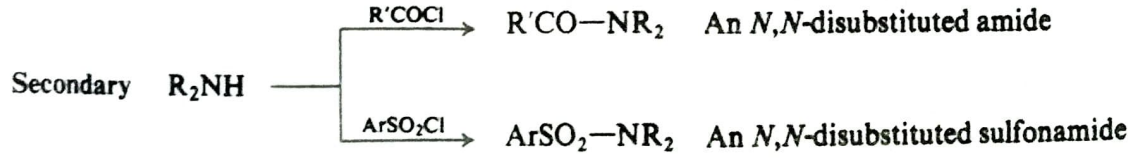
Examples:

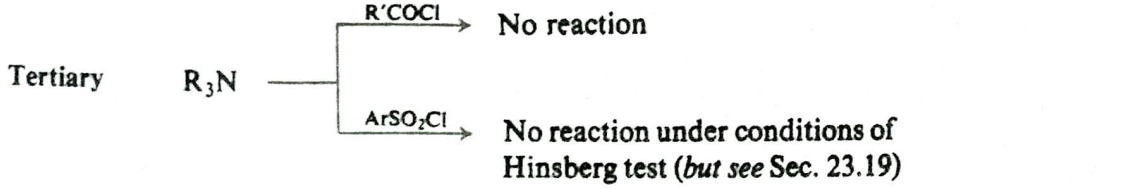




3. Conversion into amides. Discussed in Sec. 23.7.







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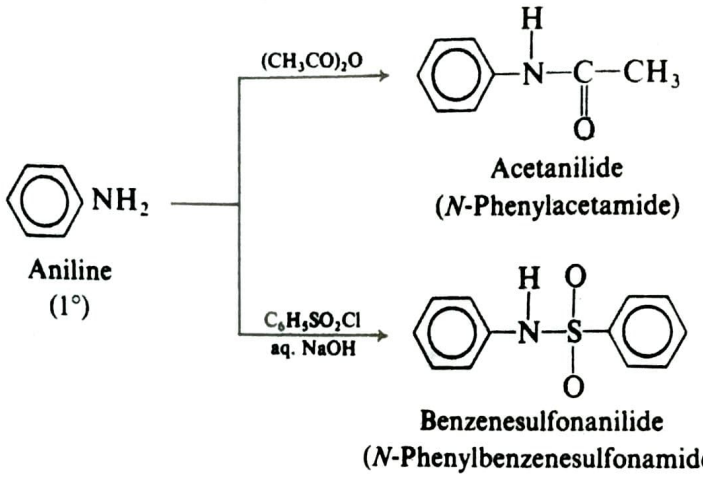
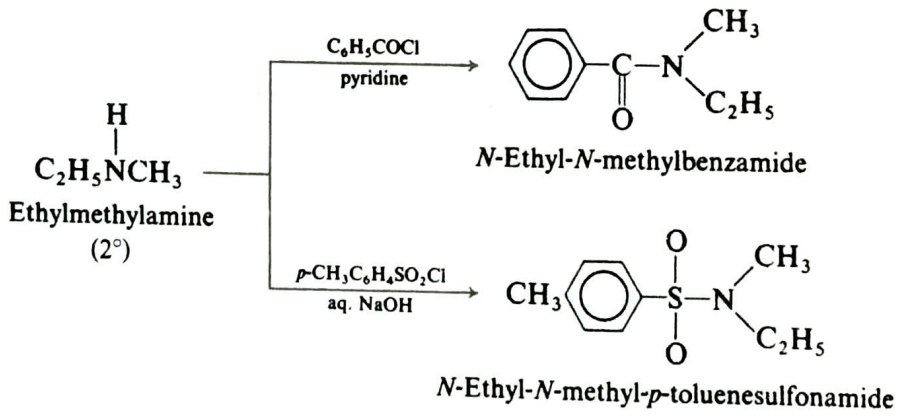
Examples:



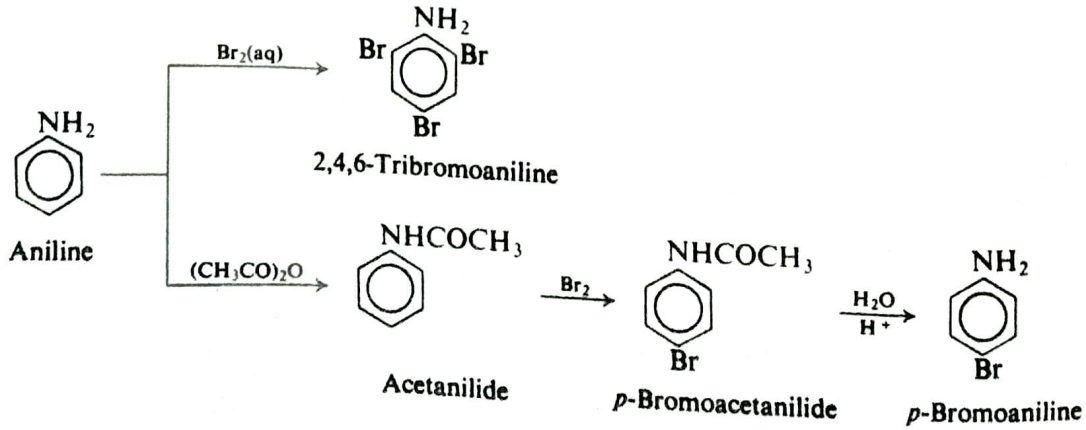


4. Ring substitution in aromatic amines. Discussed in Secs. 23.8, 23.11 and 23.18.

$-NH_2$, $-NHR$, $-NR_2$: Activate powerfully, and direct *ortho,para* in electrophilic aromatic substitution

$-NHCOR$: Less powerful activator than $-NH_2$

Examples:



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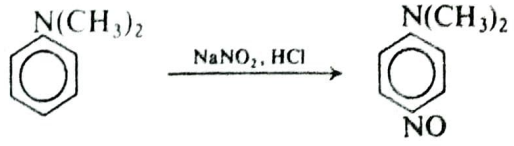
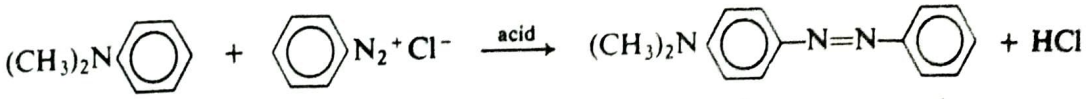
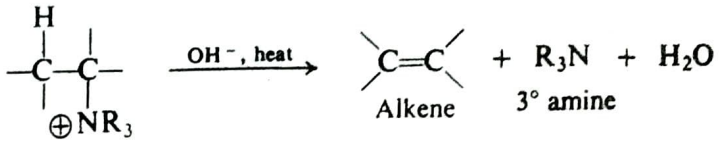


N,N-Dimethylaniline — *p*-Nitroso-*N,N*-dimethylaniline



N,N-Dimethylaniline — Benzenediazonium chloride — An azo compound

5. Hofmann elimination from quaternary ammonium salts. Discussed in Secs. 23.5–23.6.



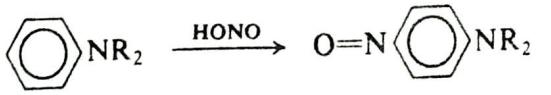
Quaternary ammonium ion — Alkene — 3° amine

6. Reactions with nitrous acid. Discussed in Secs. 23.11–23.12.

Primary aromatic $ArNH_2 \xrightarrow{HONO} Ar{-}N{\equiv}N^+$ Diazonium salt

Primary aliphatic $RNH_2 \xrightarrow{HONO} [R{-}N{\equiv}N^+] \xrightarrow{H_2O} N_2 +$ mixture of alcohols and alkenes

Secondary aromatic or aliphatic ArNHR or $R_2NH \xrightarrow{HONO}$ $Ar{-}\underset{\displaystyle R}{\overset{\displaystyle |}{N}}{-}N{=}O$ or $R_2N{-}N{=}O$ *N*-Nitrosoamine

Tertiary aromatic  *p*-Nitroso compound ■

23.2 Basicity of amines. Basicity constant

Like ammonia, amines are converted into their salts by aqueous mineral acids and are liberated from their salts by aqueous hydroxides. Like ammonia, therefore, amines are more basic than water and less basic than hydroxide ion:

$$\underset{\text{Stronger base}}{RNH_2} + H_3O^+ \longrightarrow \underset{\text{Weaker base}}{RNH_3^+} + H_2O$$

$$RNH_3^+ + \underset{\text{Stronger base}}{OH} \longrightarrow \underset{\text{Weaker base}}{RNH_2} + H_2O$$

We found it convenient to compare acidities of carboxylic acids by measuring the extent to which they give up hydrogen ion to water; the equilibrium constant for this reaction we combined with $[H_2O]$ to obtain the acidity constant, K_a. In the same way, it is convenient to compare basicities of amines by measuring the extent to which they accept hydrogen ion from water; the equilibrium constant for this reaction we combine with $[H_2O]$ to obtain the **basicity constant,** K_b.

$$RNH_2 + H_2O \rightleftharpoons RNH_3^+ + OH^-$$

$$K_b = K_{eq}[H_2O] = \frac{[RNH_3^+][OH^-]}{[RNH_2]}$$

Each amine has its characteristic K_b; the larger the K_b, the stronger the base.

We must not lose sight of the fact that the principal base in an aqueous solution of an amine (or of ammonia, for that matter) is the *amine* itself, not hydroxide ion. Measurement of $[OH^-]$ is simply a convenient way to compare basicities.

We see in Table 22.1 (p. 824) that aliphatic amines of all three classes have K_b values of about 10^{-3} to 10^{-4} (0.001 to 0.0001); they are thus somewhat stronger bases than ammonia ($K_b = 1.8 \times 10^{-5}$). Aromatic amines, on the other hand, are considerably weaker bases than ammonia, having K_b values of 10^{-9} or less. Substituents on the ring have a marked effect on the basicity of aromatic amines, *p*-nitroaniline, for example, being only 1/4000 as basic as aniline (Table 23.1).

Table 23.1 BASICITY CONSTANTS OF SUBSTITUTED ANILINES

		K_b of aniline $= 4.2 \times 10^{-10}$			
	K_b		K_b		K_b
p-NH_2	140×10^{-10}	*m*-NH_2	10×10^{-10}	*o*-NH_2	3×10^{-10}
p-OCH_3	20×10^{-10}	*m*-OCH_3	2×10^{-10}	*o*-OCH_3	3×10^{-10}
p-CH_3	12×10^{-10}	*m*-CH_3	5×10^{-10}	*o*-CH_3	2.6×10^{-10}
p-Cl	1×10^{-10}	*m*-Cl	0.3×10^{-10}	*o*-Cl	0.05×10^{-10}
p-NO_2	0.001×10^{-10}	*m*-NO_2	0.029×10^{-10}	*o*-NO_2	0.00006×10^{-10}

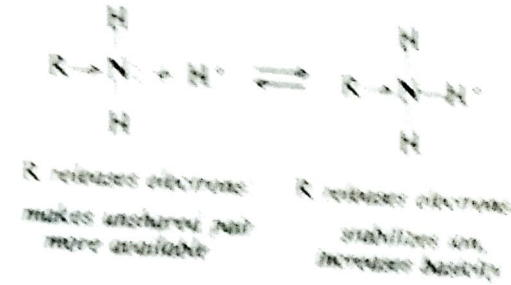
23.3 Structure and basicity

Let us see how basicity of amines is related to structure. We shall handle basicity just as we handled acidity: we shall compare the stabilities of amines with the stabilities of their ions; the more stable the ion relative to the amine from which it is formed, the more basic the amine.

First of all, amines are more basic than alcohols, ethers, esters, etc., for the same reason that ammonia is more basic than water: nitrogen is less electronegative than oxygen, and can better accommodate the positive charge of the ion.

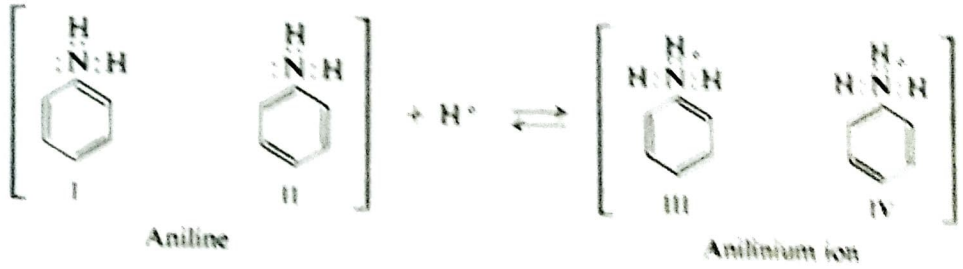
An aliphatic amine is more basic than ammonia because the electron-releasing alkyl groups tend to disperse the positive charge of the substituted ammonium ion, and therefore stabilize it in a way that is not possible for the unsubstituted ammonium ion. Thus an ammonium ion is stabilized by electron release in the

same way as a carbocation (Sec. 5.20). From another point of view, we can consider that an alkyl group pushes electrons toward nitrogen, and thus makes the fourth pair more available for sharing with an acid. (The differences in basicity among primary, secondary, and tertiary aliphatic amines are due to a combination of solvation and polar factors.)



How can we account for the fact that aromatic amines are weaker bases than ammonia? Let us compare the structures of aniline and the anilinium ion with the structures of ammonia and the ammonium ion. We see that ammonia and the ammonium ion are each represented satisfactorily by a single structure:

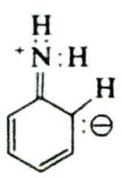
Aniline and anilinium ion contain the benzene ring and therefore are hybrids of the Kekulé structures I and II, and III and IV. This resonance presumably stabilizes



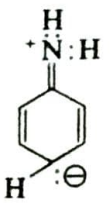
both amine and ion to the same extent. It lowers the energy content of each by the same number of kilocalories per mole, and hence does not affect the *difference* in their energy contents, that is, does not affect ΔG of ionization. If there were no other factors involved, then, we might expect the basicity of aniline to be about the same as the basicity of ammonia.

However, there are additional structures to be considered. To account for the powerful activating effect of the $-NH_2$ group on electrophilic aromatic substitution (Sec. 15.18), we considered that the intermediate carbocation is stabilized by structures in which there is a double bond between nitrogen and the ring; contribution from these structures is simply a way of indicating the tendency for nitrogen to share its fourth pair of electrons and to accept a positive charge. The $-NH_2$ group tends to share electrons with the ring, not only in the carbocation that is the intermediate in electrophilic aromatic substitution, but also in the aniline molecule itself.

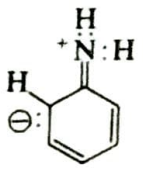
Thus aniline is a hybrid not only of structures I and II but also of structures V, VI, and VII. We cannot draw comparable structures of the anilinium ion.



V



VI



VII

Contribution from the three structures V, VI, and VII stabilizes the amine in a way that is not possible for the ammonium ion; resonance thus lowers the energy content of aniline more than it lowers the energy content of the anilinium ion. The net effect is to shift the equilibrium in the direction of less ionization, that is, to make K_b smaller (Fig. 23.2). (See, however, the discussion in Sec. 19.11.)

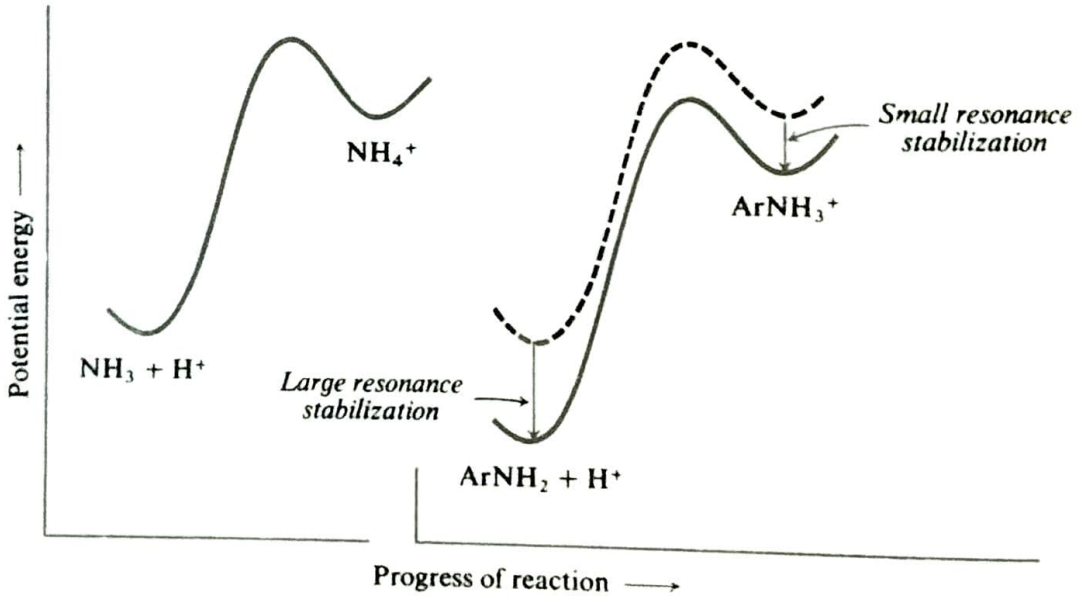


Figure 23.2 Molecular structure and position of equilibrium. A resonance-stabilized aromatic amine is a weaker base than ammonia. (The plots are aligned with each other for easy comparison.)

The low basicity of aromatic amines is thus due to the fact that the amine is stabilized by resonance to a greater extent than is the ion.

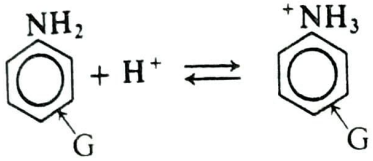
From another point of view, we can say that aniline is a weaker base than ammonia because the fourth pair of electrons is partly shared with the ring and is thus less available for sharing with a hydrogen ion. The tendency (through resonance) for the $-NH_2$ group to release electrons to the aromatic ring makes the ring more reactive toward electrophilic attack; at the same time this tendency necessarily makes the amine less basic. Similar considerations apply to other aromatic amines.

23.4 Effect of substituents on basicity of aromatic amines

How is the basicity of an aromatic amine affected by substituents on the ring?

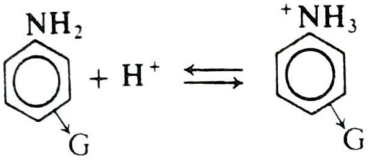
In Table 23.1 (p. 850) we see that an electron-releasing substituent like $-CH_3$ increases the basicity of aniline, and an electron-withdrawing substituent like $-X$ or $-NO_2$ decreases the basicity. These effects are understandable. Electron release tends to disperse the positive charge of the anilinium ion, and thus stabilizes the ion relative to the amine. Electron withdrawal tends to intensify the positive charge of the anilinium ion, and thus destabilizes the ion relative to the amine.

Basicity of aromatic amines



G releases electrons:
stabilizes cation,
increases basicity

G = $-NH_2$
$-OCH_3$
$-CH_3$



G withdraws electrons:
destabilizes cation,
decreases basicity

G = $-NH_3^+$
$-NO_2$
$-SO_3^-$
$-COOH$
$-X$

We notice that the base-strengthening substituents are the ones that activate an aromatic ring toward electrophilic substitution; the base-weakening substituents are the ones that deactivate an aromatic ring toward electrophilic substitution (see Sec. 15.5). Basicity depends upon position of equilibrium, and hence on relative stabilities of reactants and products. Reactivity in electrophilic aromatic substitution depends upon rate, and hence on relative stabilities of reactants and transition state. The effect of a particular substituent is the same in both cases, however, since the controlling factor is accommodation of a positive charge.

A given substituent affects the basicity of an amine and the acidity of a carboxylic acid in opposite ways (compare Sec. 19.14). This is to be expected, since basicity depends upon ability to accommodate a positive charge, and acidity depends upon ability to accommodate a negative charge.

Once again we see the operation of the **ortho effect** (Sec. 19.14). Even electron-releasing substituents weaken basicity when they are *ortho* to the amino group, and electron-withdrawing substituents do so to a much greater extent from the *ortho* position than from the *meta* or *para* position.

From another point of view, we can consider that an electron-releasing group pushes electrons toward nitrogen and makes the fourth pair more available for sharing with an acid, whereas an electron-withdrawing group helps pull electrons away from nitrogen and thus makes the fourth pair less available for sharing.

Problem 23.1 (a) Besides destabilizing the anilinium ion, how else might a nitro group affect basicity? (*Hint*: See structures V–VII on p. 852.) (b) Why does the nitro group exert a larger base-weakening effect from the *para* position than from the nearer *meta* position?

Problem 23.2 Draw the structural formula of the product expected (if any) from the reaction of trimethylamine and BF_3.

23.5 Quaternary ammonium salts. Hofmann elimination

Like ammonia, an amine can react with an alkyl halide; the product is an amine of the next higher class. The alkyl halide undergoes nucleophilic substitution, with the basic amine serving as the nucleophilic reagent. We see that one of the

$$\underset{1^\circ}{RNH_2} \xrightarrow{RX} \underset{2^\circ}{R_2NH} \xrightarrow{RX} \underset{3^\circ}{R_3N} \xrightarrow{RX} \underset{4^\circ}{R_4N^+X^-}$$

hydrogens attached to nitrogen has been replaced by an alkyl group; the reaction is therefore often referred to as *alkylation of amines*. The amine can be aliphatic or aromatic, primary, secondary, or tertiary; the halide is generally an alkyl halide.

We have already encountered alkylation of amines as a side reaction in the preparation of primary amines by the ammonolysis of halides (Sec. 22.10), and as a method of synthesis of secondary and tertiary amines (Sec. 22.13). Let us look at one further aspect of this reaction, the formation of quaternary ammonium salts.

Quaternary ammonium salts are the products of the final stage of alkylation of nitrogen. They have the formula $R_4N^+X^-$. Four organic groups are covalently bonded to nitrogen, and the positive charge of this ion is balanced by some negative ion. When the salt of a primary, secondary, or tertiary amine is treated with hydroxide ion, nitrogen gives up a hydrogen ion and the free amine is liberated. The quaternary ammonium ion, having no proton to give up, is not affected by hydroxide ion.

When a solution of a quaternary ammonium halide is treated with silver oxide, silver halide precipitates. When the mixture is filtered and the filtrate is evaporated to dryness, there is obtained a solid which is free of halogen. An aqueous solution of this substance is strongly alkaline, and is comparable to a solution of sodium hydroxide or potassium hydroxide. A compound of this sort is called a **quaternary ammonium hydroxide**. It has the structure $R_4N^+OH^-$. Its aqueous solution is basic for the same reason that solutions of sodium or potassium hydroxide are basic: the solution contains hydroxide ions.

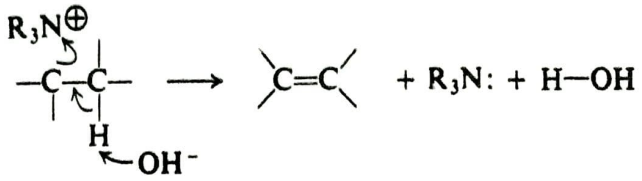
$$\underset{\text{Quaternary ammonium salt}}{R:\overset{\overset{R}{\cdot\cdot}}{\underset{\underset{R}{\cdot\cdot}}{N}}:R^+X^-} \xrightarrow{Ag_2O} \underset{\text{Quaternary ammonium hydroxide}}{R:\overset{\overset{R}{\cdot\cdot}}{\underset{\underset{R}{\cdot\cdot}}{N}}:R^+OH^-} + \underset{\textit{Insoluble}}{AgX}$$

When a quaternary ammonium hydroxide is heated strongly (to 125 °C or higher), it decomposes to yield water, a tertiary amine, and an alkene. Trimethyl-*n*-propylammonium hydroxide, for example, yields trimethylamine and propylene:

$$\underset{\text{Trimethyl-}n\text{-propylammonium hydroxide}}{CH_3-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{N^+}}-CH_2CH_2CH_3\ OH^-} \xrightarrow{heat} \underset{\text{Trimethylamine}}{CH_3-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{N}}} + \underset{\text{Propylene}}{CH_2{=}CHCH_3} + H_2O$$

This reaction, called the **Hofmann elimination**, is quite analogous to the dehydrohalogenation of an alkyl halide (Sec. 8.13). Most commonly, reaction is E2:

hydroxide ion abstracts a proton from carbon; a molecule of tertiary amine is expelled, and the double bond is generated. Bases other than hydroxide ion can be used.



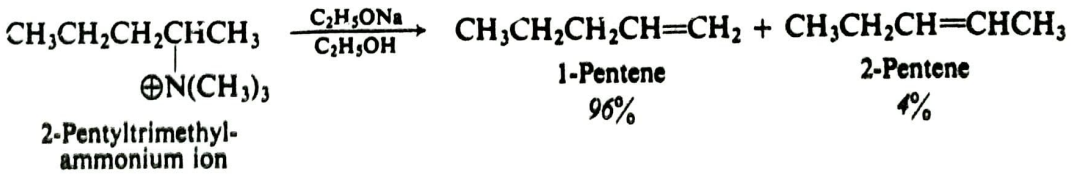
E1 elimination from quaternary ammonium ions is also known. Competing with either E2 or E1 elimination there is, as usual, substitution: either S_N2 or S_N1. (*Problem*: What products would you expect from substitution?)

The formation of quaternary ammonium salts, followed by an elimination of the kind just described and identification of the alkene and tertiary amine formed, was once used in the determination of the structure of complicated amines.

23.6 E2 elimination: Hofmann orientation. The variable E2 transition state

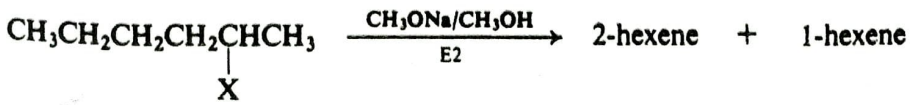
Where the structure permits, E2 elimination can produce a mixture of isomers; which one predominates is determined by the orientation of the elimination. In dehydrohalogenation, we saw (Sec. 8.20), the orientation is *Saytzeff*: the preferred product is the more highly branched alkene which, as we saw, is the more stable one. Orientation, we said, is controlled by the alkene character of the transition state.

What is the orientation of the Hofmann elimination? A single example will show us the kind of thing that is observed:



We see that the preferred product here is the *least* branched alkene, 1-pentene. Such orientation is called **Hofmann orientation**, since it was first observed by Hofmann in studying this particular kind of reaction.

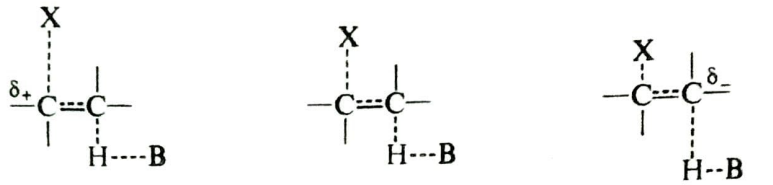
Both polar and steric factors have been proposed to account for Hofmann orientation. To see how the polar factor would apply, let us return to dehydrohalogenation and take, as an example, elimination from the 2-hexyl halides brought about by the strong base sodium methoxide. The iodide, bromide, and chloride react with Saytzeff orientation, but the fluoride gives predominantly the less substituted alkene, 1-hexene, that is, reacts with Hofmann orientation. Furthermore, we can see that there is a steady increase in the fraction of 1-hexene along the series I, Br, Cl, F.



X = I	81%	19%
Br	72	28
Cl	67	33
F	30	70

Such observations are best understood in terms of what Bunnett (p. 299) has called the *variable transition state* theory of E2 elimination. We are speaking, remember, of a one-step elimination; both the C—H and C—X bonds are being broken in the same transition state. But there is a whole spectrum of E2 transition states which differ in the relative *extent* to which the two bonds are broken.

Variable E2 transition state



Carbocation-like | Central | Carbanion-like

Much alkene character

At the center of the spectrum is the transition state we have described before for elimination from alkyl halides: both C—H and C—X bonds are broken to a considerable extent, the transition state has considerable alkene character, and orientation is Saytzeff.

But, if breaking of the C—H bond greatly exceeds breaking of the C—X bond, there is little alkene character to the transition state, but instead the development of negative charge on the carbon losing the proton. In this case, the transition state has *carbanion character*, and its stability is controlled as we might expect, by dispersal or intensification of the negative charge: electron-withdrawing groups stabilize, and electron-releasing groups destabilize. At one end of the spectrum, then, we have the carbanion-like transition state.

Consider elimination from the 2-hexyl halides. With the iodide, there is considerable breaking of both bonds in the transition state, much alkene character, and preferred formation of the more stable alkene: Saytzeff orientation. As we go along the series I, Br, Cl, F, the C—X bond becomes stronger, and the extent to which it is broken in the transition state decreases. At the same time, the electron-withdrawing effect of X increases, favoring the development of negative charge. With the fluoride, we have predominant C—H bond-breaking, with little alkene character but considerable carbanion character to the transition state. A primary hydrogen is preferentially abstracted by base, since that permits the negative charge to develop on a primary carbon, to which there is attached only one electron-releasing alkyl group. Orientation is Hofmann.

Bunnett believes that C—F bond-breaking lags behind C—H bond-breaking chiefly because of the strength of the C—F bond. Ingold (p. 179), who was the first to suggest carbanion character as the underlying cause of Hofmann orientation, believed that electron withdrawal by fluorine is the major factor.

On this basis, how do we account for Hofmann orientation in the E2 elimination from quaternary ammonium salts? Here, the transition state has considerable carbanion character, at least partly because powerful electron withdrawal by the positively charged nitrogen favors development of negative charge. There is preferential abstraction of a proton from the carbon that can best accommodate the partial negative charge: in the example given, from the primary carbon rather than the secondary.

Alternatively, steric factors have been proposed as the main cause of Hofmann orientation. The large size of the leaving group, R_3N, gives crowding in the transition state; a proton on the less substituted carbon is more accessible, and is preferentially abstracted by the base.

It seems likely that *both* factors, polar and steric, are involved.

The stereochemistry of Hofmann elimination is commonly *anti*, but less so than was formerly believed. *syn*-Elimination is important for certain cyclic compounds, and can be made important even for open-chain compounds by the proper choice of base and solvent. Quaternary ammonium ions are more prone to *syn*-elimination than alkyl halides and sulfonates. Electronically, *anti* formation of the double bond is favored in eliminations; but when the alkene character of the transition state is slight—as here—other factors come into play: conformational factors, it has been postulated.

Sulfonium ions, R_3S^+, react similarly to quaternary ammonium ions with regard to both orientation and stereochemistry of elimination.

Problem 23.3 Predict the major products of E2 elimination from: (a) 2-methyl-3-pentyltrimethylammonium ion; (b) diethyldi-*n*-propylammonium ion; (c) dimethylethyl(2-chloroethyl)ammonium ion; (d) dimethylethyl-*n*-propylammonium ion.

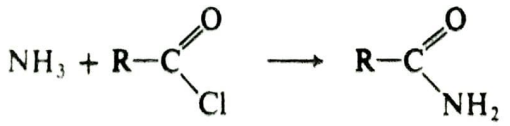
Problem 23.4 When dimethyl-*tert*-pentylsulfonium ethoxide is heated in ethanol, the alkene obtained is chiefly (86%) 2-methyl-1-butene; when the corresponding sulfonium iodide is heated in ethanol, the alkene obtained is chiefly (86%) 2-methyl-2-butene.

(a) How do you account for the difference in products? (b) From the sulfonium iodide reaction there is also obtained considerable material identified as an ether. What ether would you expect it to be, and how is it formed? (c) What ether would you expect to obtain from the sulfonium ethoxide reaction?

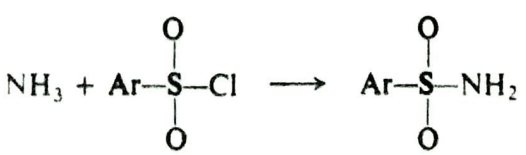
Problem 23.5 2-Phenylethyl bromide undergoes E2 elimination about 10 times as fast as 1-phenylethyl bromide even though they both yield the same alkene. Suggest a possible explanation for this.

23.7 Conversion of amines into substituted amides

We have learned (Sec. 20.11) that ammonia reacts with acid chlorides of carboxylic acids to yield amides, compounds in which —Cl has been replaced by



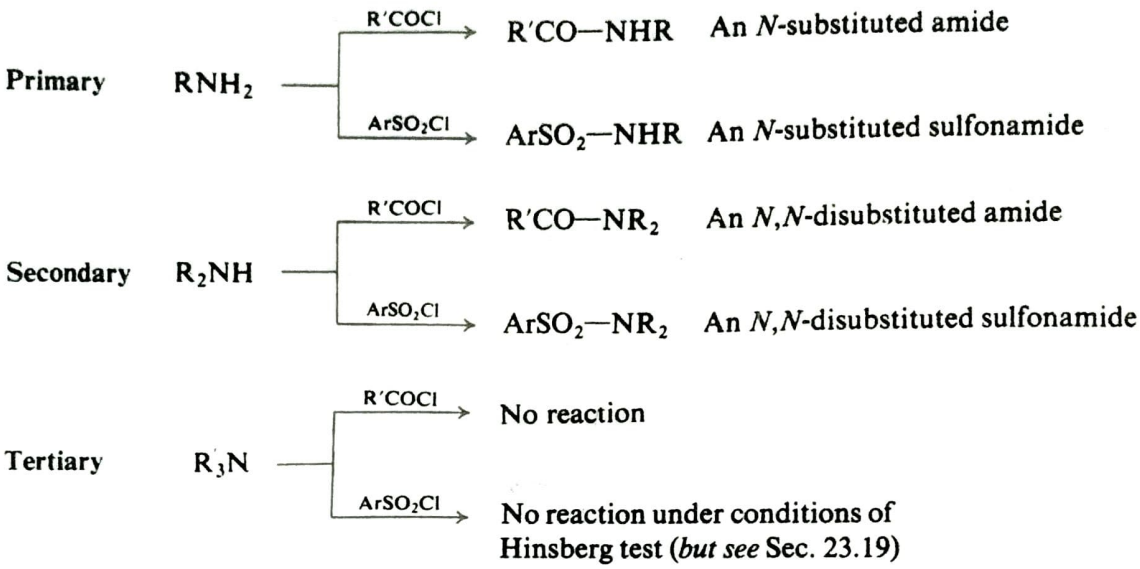
the $-NH_2$ group. Not surprisingly, acid chlorides of sulfonic acids react similarly.



A sulfonyl chloride A sulfonamide

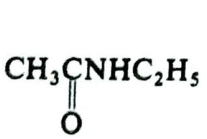
In these reactions ammonia serves as a nucleophilic reagent, attacking the carbonyl carbon or sulfur and displacing chloride ion. In the process nitrogen loses a proton to a second molecule of ammonia or another base.

In a similar way primary and secondary amines can react with acid chlorides to form **substituted amides**, compounds in which —Cl has been replaced by the —NHR or $-NR_2$ group:

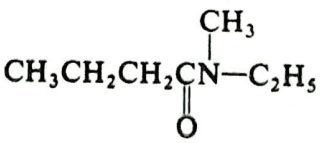


Tertiary amines, although basic and hence nucleophilic, fail to yield amides, presumably because they cannot lose a proton (to stabilize the product) after attaching themselves to carbon or to sulfur. Here is a reaction which requires not only that amines be nucleophilic, but also that they possess a hydrogen atom attached to nitrogen. (However, see Sec. 23.19.)

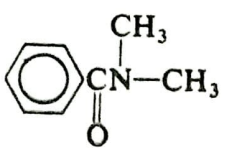
Substituted amides are generally named as derivatives of the unsubstituted amides. For example:



N-Ethylacetamide



N-Ethyl-*N*-methylbutyramide



N,*N*-Dimethylbenzamide

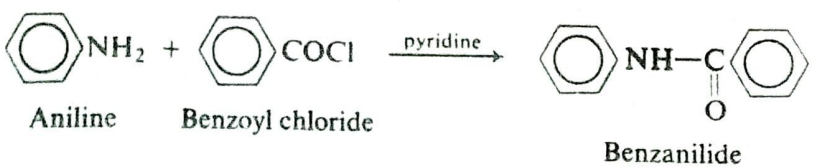
In many cases, and particularly where aromatic amines are involved, we are more interested in the amine from which the amide is derived than in the acyl group. In these cases the substituted amide is named as an acyl derivative of the amine. For example:

Acetanilide

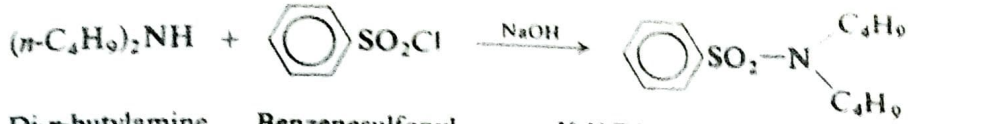
Benzanilide

Aceto-*p*-toluidide

Substituted amides of aromatic carboxylic acids or of sulfonic acids are prepared by the Schotten–Baumann technique: the acid chloride is added to the amine in the presence of a base, either aqueous sodium hydroxide or pyridine. For example:

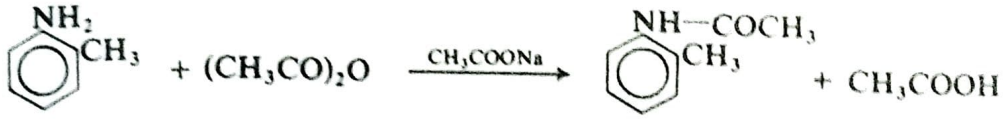


Aniline Benzoyl chloride Benzanilide



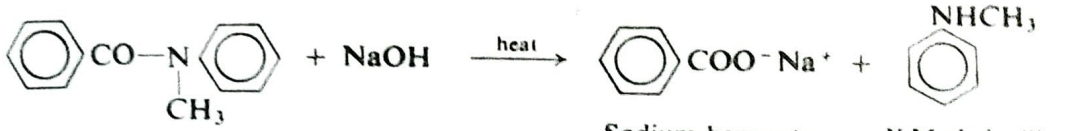
Di-*n*-butylamine Benzenesulfonyl chloride *N*,*N*-Di-*n*-butylbenzenesulfonamide

Acetylation is generally carried out using acetic anhydride rather than acetyl chloride. For example:

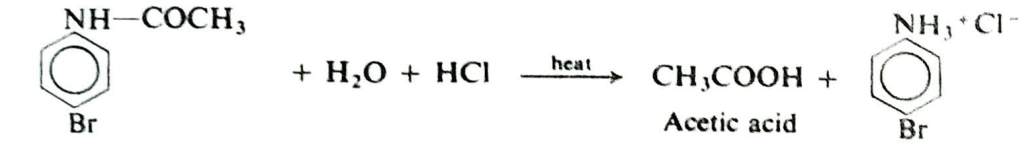


o-Toluidine Acetic anhydride Aceto-*o*-toluidide

Like simple amides, substituted amides undergo hydrolysis; the products are the acid and the amine, although one or the other is obtained as its salt, depending upon the acidity or alkalinity of the medium.

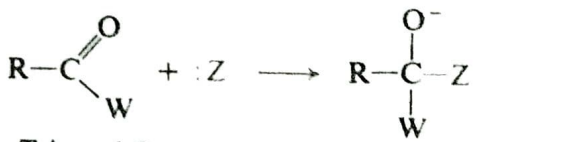


N-Methylbenzanilide Sodium benzoate *N*-Methylaniline



p-Bromoacetanilide Acetic acid *p*-Bromoanilinium chloride

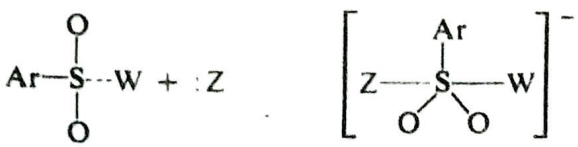
Sulfonamides are hydrolyzed more slowly than amides of carboxylic acids; examination of the structures involved shows us what probably underlies this difference. Nucleophilic attack on a trigonal acyl carbon (Sec. 20.4) is relatively unhindered; it involves the temporary attachment of a fourth group, the nucleophilic reagent. Nucleophilic attack on tetrahedral sulfonyl sulfur is relatively hindered; it involves the temporary attachment of a *fifth* group. The tetrahedral carbon of the acyl intermediate makes use of the permitted octet of electrons; although sulfur may be able to use more than eight electrons in covalent bonding,



Trigonal C
Attack relatively unhindered

Tetrahedral C
Stable octet

Acyl nucleophilic substitution



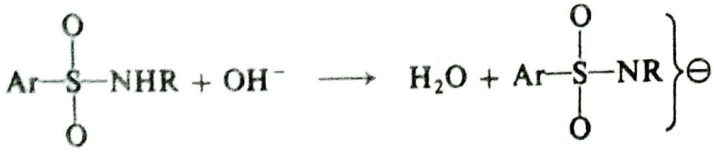
Tetrahedral S
Attack hindered

Pentavalent S
Unstable decet

Sulfonyl nucleophilic substitution

this is a less stable system than the octet. Thus both steric and electronic factors tend to make sulfonyl compounds less reactive than acyl compounds.

There is a further contrast between the amides of the two kinds of acids. The substituted amide from a primary amine still has a hydrogen attached to nitrogen, and as a result is *acidic*: in the case of a sulfonamide, this acidity is appreciable, and much greater than for the amide of a carboxylic acid. A monosubstituted sulfonamide is less acidic than a carboxylic acid, but about the same as a phenol (Sec. 24.9); it reacts with aqueous hydroxides to form salts.



This difference in acidity, too, is understandable. A sulfonic acid is more acidic than a carboxylic acid because the negative charge of the anion is dispersed over three oxygens instead of just two. In the same way, a sulfonamide is more acidic than the amide of a carboxylic acid because the negative charge is dispersed over two oxygens plus nitrogen instead of over just one oxygen plus nitrogen.

Problem 23.6 (a) Although amides of carboxylic acids are very weakly acidic ($K_a = 10^{-14}$ to 10^{-15}), they are still enormously more acidic than ammonia ($K_a = 10^{-33}$) or amines, RNH_2. Account in detail for this.

(b) Diacetamide, $(CH_3CO)_2NH$, is much more acidic ($K_a = 10^{-11}$) than acetamide ($K_a = 8.3 \times 10^{-16}$), and roughly comparable to benzenesulfonamide ($K_a = 10^{-10}$). How can you account for this?

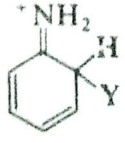
Problem 23.7 In contrast to carboxylic esters, we know, alkyl sulfonates undergo nucleophilic attack at alkyl carbon. What *two* factors are responsible for this difference

in behavior? (*Hint*: See Sec. 5.8.)

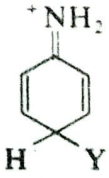
The conversion of an amine into a sulfonamide is used in determining the class of the amine; this is discussed in the section on analysis (Sec. 23.19).

23.8 Ring substitution in aromatic amines

We have already seen that the $-NH_2$, $-NHR$, and $-NR_2$ groups act as powerful activators and *ortho,para* directors in electrophilic aromatic substitution. These effects were accounted for by assuming that the intermediate carbocation is stabilized by structures like I and II in which nitrogen bears a positive charge and



I



II

is joined to the ring by a double bond. Such structures are especially stable since in them every atom (except hydrogen) has a complete octet of electrons; indeed, structure I or II *by itself* must pretty well represent the intermediate.

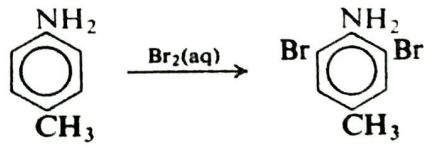
In such structures nitrogen shares more than one pair of electrons with the ring, and hence carries the charge of the "carbocation". Thus the basicity of nitrogen accounts for one more characteristic of aromatic amines.

The acetamido group, $-NHCOCH_3$, is also activating and *ortho,para*-directing, but less powerfully so than a free amino group. Electron withdrawal by oxygen of the carbonyl group makes the nitrogen of an amide a much poorer source of electrons than the nitrogen of an amine. Electrons are less available for sharing with a hydrogen ion, and therefore amides are much weaker bases than amines: amides of carboxylic acids do not dissolve in dilute aqueous acids. Electrons are less available for sharing with an aromatic ring, and therefore an acetamido group activates an aromatic ring less strongly than an amino group.

More precisely, electron withdrawal by carbonyl oxygen destabilizes a positive charge on nitrogen, whether this charge is acquired by *protonation* or by *electrophilic attack on the ring*.

(We have seen (Sec. 15.5) that the $-NR_3^+$ group is a powerful deactivator and *meta* director. In a quaternary ammonium salt, nitrogen no longer has electrons to share with the ring; on the contrary, the full-fledged positive charge on nitrogen makes the group strongly electron-attracting.)

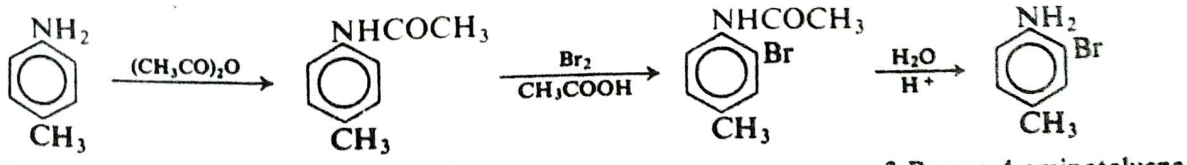
In electrophilic substitution, the chief problem encountered with aromatic amines is that they are *too* reactive. In halogenation, substitution tends to occur at every available *ortho* or *para* position. For example:



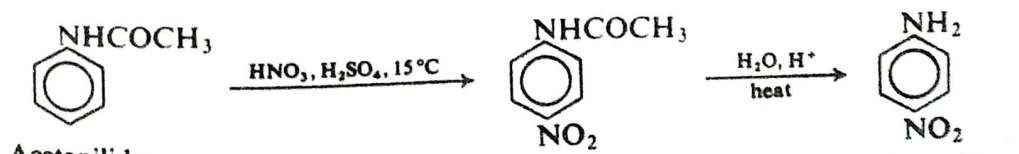
p-Toluidine 3,5-Dibromo-4-aminotoluene

Nitric acid not only nitrates, but oxidizes the highly reactive ring as well, with loss of much material as tar. Furthermore, in the strongly acidic nitration medium, the amine is converted into the anilinium ion; substitution is thus controlled not by the $-NH_2$ group but by the $-NH_3^+$ group which, because of its positive charge, directs much of the substitution to the *meta* position.

There is, fortunately, a simple way out of these difficulties. We *protect* the amino group: we acetylate the amine, then carry out the substitution, and finally hydrolyze the amide to the desired substituted amine. For example:



p-Toluidine Aceto-*p*-toluidide 3-Bromo-4-aminotoluene

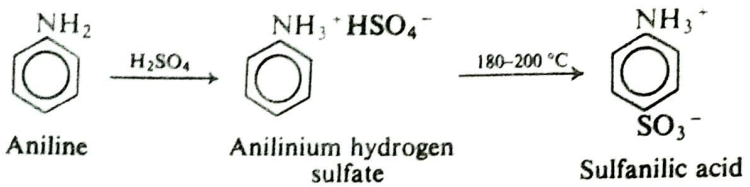


Acetanilide *p*-Nitroacetanilide *p*-Nitroaniline

Problem 23.8 Nitration of un-acetylated aniline yields a mixture of about two-thirds *meta* and one-third *para* product. Since almost all the aniline is in the form of the anilinium ion, how do you account for the fact that even more *meta* product is not obtained?

23.9 Sulfonation of aromatic amines. Dipolar ions

Aniline is usually sulfonated by "baking" the salt, anilinium hydrogen sulfate, at 180–200 °C; the chief product is the *para* isomer. In this case we cannot discuss orientation on our usual basis of which isomer is formed *faster*. Sulfonation is



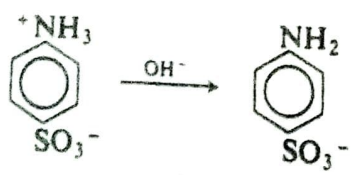
Aniline — Anilinium hydrogen sulfate — Sulfanilic acid

known to be reversible, and the *para* isomer is known to be the most stable isomer; it may well be that the product obtained, the *para* isomer, is determined by the position of an equilibrium and not by relative rates of formation (see Sec. 11.23 and Sec. 16.12). It also seems likely that, in some cases at least, sulfonation of amines proceeds by a mechanism that is entirely different from ordinary aromatic substitution.

Whatever the mechanism by which it is formed, the chief product of this reaction is *p*-aminobenzenesulfonic acid, known as **sulfanilic acid**; it is an important and interesting compound.

First of all, its properties are not those we would expect of a compound containing an amino group and a sulfonic acid group. Both aromatic amines and aromatic sulfonic acids have low melting points; benzenesulfonic acid, for example, melts at 66 °C, and aniline at −6 °C. Yet sulfanilic acid has such a high melting point that on being heated it decomposes (at 280–300 °C) before its melting point can be reached. Sulfonic acids are generally very soluble in water; indeed, we have seen that the sulfonic acid group is often introduced into a molecule to make it water-soluble. Yet sulfanilic acid is not only insoluble in organic solvents, but also nearly insoluble in water. Amines dissolve in aqueous mineral acids because of their conversion into water-soluble salts. Sulfanilic acid is soluble in aqueous bases but insoluble in aqueous acids.

These properties of sulfanilic acid are understandable when we realize that sulfanilic acid actually has the structure I which contains the $-NH_3^+$ and $-SO_3^-$ groups. Sulfanilic acid is a salt, but of a rather special kind, called a **dipolar ion** (sometimes called a *zwitterion*, from the German, *Zwitter*, hermaphrodite). It is the product of reaction between an acidic group and a basic group that are part of the same molecule. The hydrogen ion is attached to nitrogen rather than oxygen



I — *Insoluble in water* — II — *Soluble in water*

simply because the $-NH_2$ group is a stronger base than the $-SO_3^-$ group. A high melting point and insolubility in organic solvents are properties we would expect of a salt. Insolubility in water is not surprising, since many salts are insoluble in water. In alkaline solution, the strongly basic hydroxide ion pulls hydrogen ion away from the weakly basic $-NH_2$ group to yield the *p*-aminobenzenesulfonate ion (II), which, like most sodium salts, is soluble in water. In aqueous acid, however, the sulfanilic acid structure is not changed, and therefore the compound remains insoluble; sulfonic acids are strong acids and their anions (very weak bases) show little tendency to accept hydrogen ion from H_3O^+.

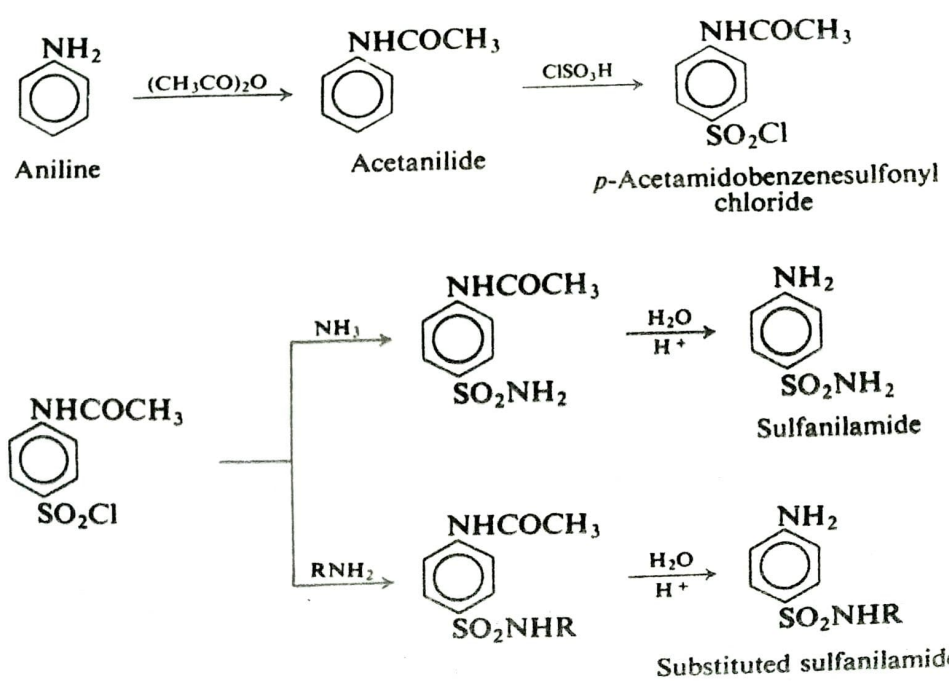
We can expect to encounter dipolar ions whenever we have a molecule containing both an amino group and an acid group, providing the amine is more basic than the anion of the acid.

Problem 23.9 *p*-Aminobenzoic acid is not a dipolar ion, whereas glycine (aminoacetic acid) is a dipolar ion. How can you account for this?

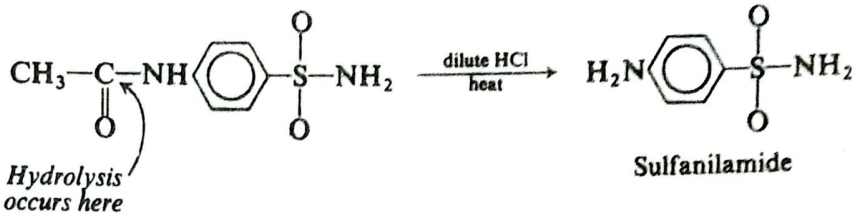
23.10 Sulfanilamide. The sulfa drugs

The amide of sulfanilic acid (*sulfanilamide*) and certain related substituted amides are of considerable medical importance as the *sulfa drugs*. Although they have been supplanted to a wide extent by the antibiotics (such as penicillin, terramycin, chloromycetin, and aureomycin), the sulfa drugs still have their medical uses, and make up a considerable portion of the output of the pharmaceutical industry.

Sulfonamides are prepared by the reaction of a sulfonyl chloride with ammonia or an amine. The presence in a sulfonic acid molecule of an amino group, however, poses a special problem: if sulfanilic acid were converted to the acid chloride, the sulfonyl group of one molecule could attack the amino group of another to form an amide linkage. This problem is solved by protecting the amino group through acetylation prior to the preparation of the sulfonyl chloride. Sulfanilamide and related compounds are generally prepared in the following way:



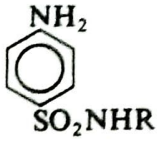
The selective removal of the acetyl group in the final step is consistent with the general observation that amides of carboxylic acids are more easily hydrolyzed than amides of sulfonic acids.



Sulfanilamide

The antibacterial activity—and toxicity—of a sulfanilamide stems from a rather simple fact: enzymes in the bacteria (and in the patients) confuse it for *p*-aminobenzoic acid, which is an essential metabolite. In what is known as ***metabolite antagonism***, the sulfanilamide competes with *p*-aminobenzoic acid for

p-Aminobenzoic acid

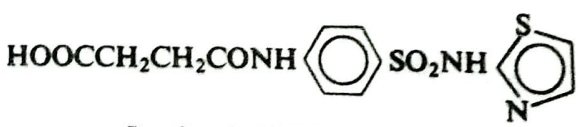


Substituted sulfanilamide

reactive sites on the enzymes; deprived of the essential metabolite, the organism fails to reproduce, and dies.

Just how good a drug the sulfanilamide is depends upon the nature of the group R attached to amido nitrogen. This group must confer just the right degree of acidity to the amido hydrogen (Sec. 23.7), but acidity is clearly only one of the factors involved. Of the hundreds of such compounds that have been synthesized, only a half dozen or so have had the proper combination of high antibacterial activity and low toxicity to human beings that is necessary for an effective drug; in nearly all these effective compounds the group R contains a heterocyclic ring (Chap. 30).

Sulfamerazine

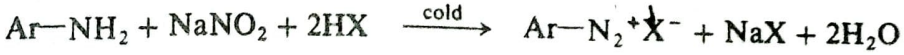


Succinoyisulfathiazole

23.11 Reactions of amines with nitrous acid

Each class of amine yields a different kind of product in its reaction with nitrous acid, HONO. This unstable reagent is generated in the presence of the amine by the action of mineral acid on sodium nitrite.

Primary aromatic amines react with nitrous acid to yield ***diazonium salts***; this is one of the most important reactions in organic chemistry. Following sections are devoted to the preparation and properties of aromatic diazonium salts.



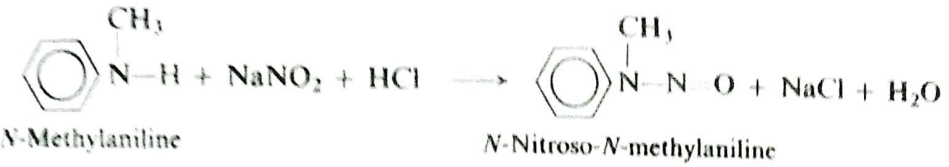
1° aromatic amine

A diazonium salt

Primary aliphatic amines also react with nitrous acid to yield diazonium salts; but since aliphatic diazonium salts are quite unstable and break down to yield a complicated mixture of organic products (see Problem 23.10, below), this reaction is of little synthetic value. The fact that nitrogen is evolved quantitatively is of some importance in analysis, however, particularly of amino acids and proteins.

$$\underset{\text{1° aliphatic amine}}{R{-}NH_2} + NaNO_2 + HX \longrightarrow \underset{\textit{Unstable}}{[R{-}N_2{}^+X^-]} \xrightarrow{H_2O} N_2 + \text{mixture of alcohols and alkenes}$$

Secondary amines, both aliphatic and aromatic, react with nitrous acid to yield *N*-nitrosoamines.



N-Methylaniline — *N*-Nitroso-*N*-methylaniline

Tertiary aromatic amines undergo ring substitution, to yield compounds in which a nitroso group, —N=O, is joined to carbon; thus *N*,*N*-dimethylaniline yields chiefly *p*-nitroso-*N*,*N*-dimethylaniline.

N,*N*-Dimethylaniline — *p*-Nitroso-*N*,*N*-dimethylaniline

Ring nitrosation is an electrophilic aromatic substitution reaction, in which the attacking reagent is either the *nitrosonium ion*, ^+NO, or some species (like $H_2O{-}NO$ or NOCl) that can easily transfer ^+NO to the ring. The nitrosonium ion is very weakly electrophilic compared with the reagents involved in nitration, sulfonation, halogenation, and the Friedel–Crafts reaction; nitrosation ordinarily occurs only in rings bearing the powerfully activating dialkylamino ($-NR_2$) or hydroxy (—OH) group. (See Fig. 23.3.)

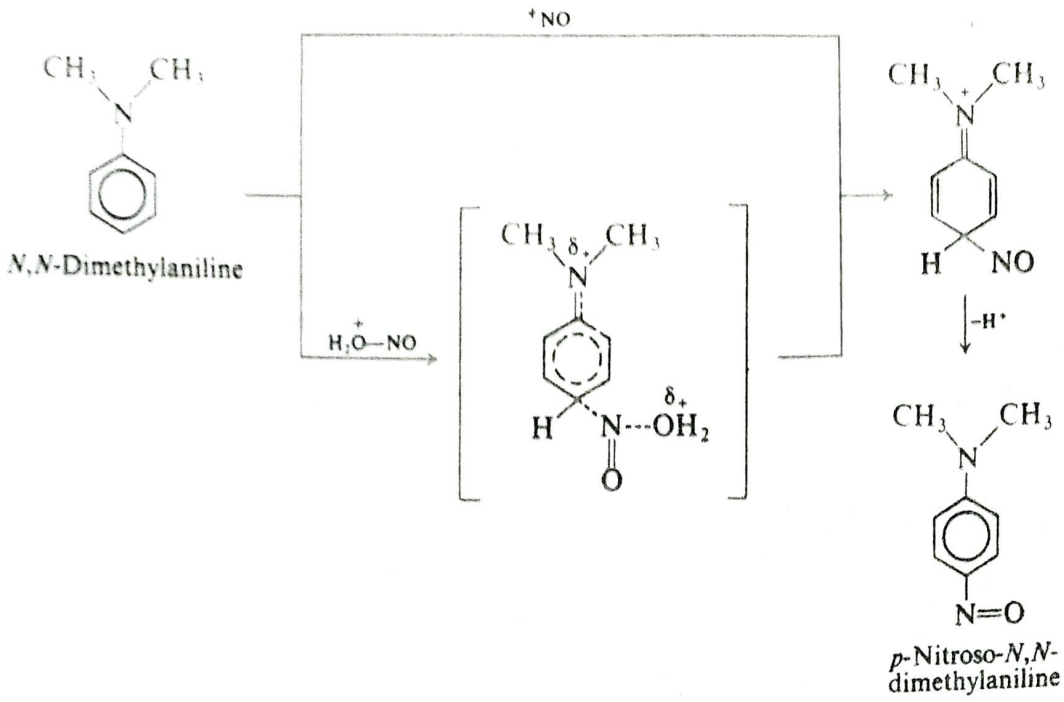


Figure 23.3 Ring nitrosation of *N*,*N*-dimethylaniline.

Despite the differences in the final product, the reaction of nitrous acid with all these amines involves the same initial step: *electrophilic attack by* ^+NO *with displacement of* H^+. This attack occurs at the position of highest electron availability in primary and secondary amines: at nitrogen. Tertiary aromatic amines are attacked at the highly reactive ring.

Problem 23.10 (a) Write equations to show how the molecule $H_2\hat{O}—NO$ is formed in the nitrosating mixture. (b) Why can this transfer ^+NO to the ring more easily than HONO can? (c) Write equations to show how NOCl can be formed from $NaNO_2$ and aqueous hydrochloric acid. (d) Why is NOCl a better nitrosating agent than HONO?

Problem 23.11 (a) Which, if either, of the following seems likely? (i) The ring of *N*-methylaniline is much less reactive toward electrophilic attack than the ring of *N,N*-dimethylaniline. (ii) Nitrogen of *N*-methylaniline is much more reactive toward electrophilic attack than nitrogen of *N,N*-dimethylaniline.

(b) How do you account for the fact that the two amines give different products with nitrous acid?

23.12 Diazonium salts. Preparation and reactions

When a primary aromatic amine, dissolved or suspended in cold aqueous mineral acid, is treated with sodium nitrite, there is formed a diazonium salt. Since

$$\underset{\substack{1^\circ \text{ aromatic}\\ \text{amine}}}{Ar—NH_2} + NaNO_2 + 2HX \xrightarrow{\text{cold}} \underset{\text{A diazonium salt}}{Ar—N{\equiv}N{:}^+X^-} + NaX + 2H_2O$$

diazonium salts slowly decompose even at ice-bath temperatures, the solution is used immediately after preparation.

The large number of reactions undergone by diazonium salts may be divided into two classes: **replacement**, in which nitrogen is lost as N_2, and some other atom or group becomes attached to the ring in its place; and **coupling**, in which the nitrogen is retained in the product.

REACTIONS OF DIAZONIUM SALTS

1. **Replacement of nitrogen**

$$Ar—N_2^+ + :Z \longrightarrow Ar—Z + N_2$$

(a) **Replacement by —Cl, —Br, and —CN. Sandmeyer reaction.** Discussed in Secs. 23.13–23.14.

$$Ar—N_2^+ \xrightarrow{CuCl} Ar—Cl + N_2$$

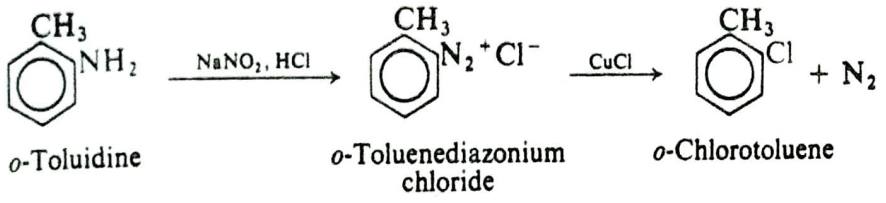
$$Ar—N_2^+ \xrightarrow{CuBr} Ar—Br + N_2$$

$$Ar—N_2^+ \xrightarrow{CuCN} Ar—CN + N_2$$

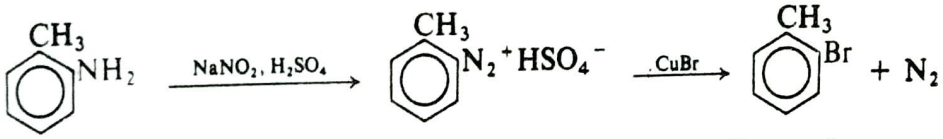
CONTINUED

CONTINUED

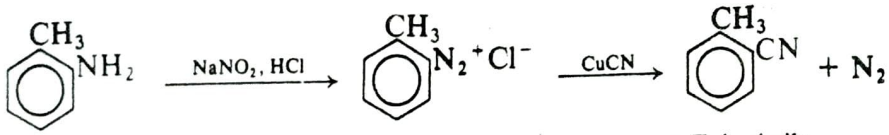
Examples:



o-Toluidine — *o*-Toluenediazonium chloride — *o*-Chlorotoluene



o-Toluidine — *o*-Bromotoluene

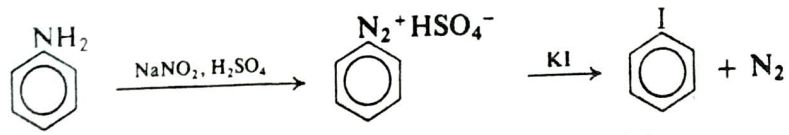


o-Toluidine — *o*-Tolunitrile

(b) **Replacement by —I. Discussed in Sec. 23.13.**

$$Ar{-}N_2^+ + I^- \longrightarrow Ar{-}I + N_2$$

Example:

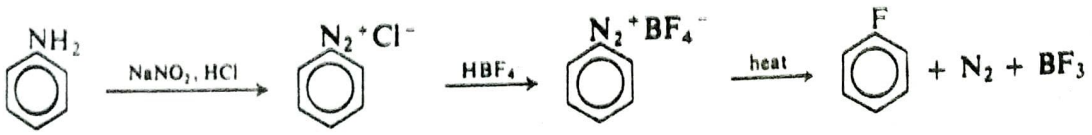


Aniline — Iodobenzene

(c) **Replacement by —F. Discussed in Sec. 23.13.**

$$Ar{-}N_2^+BF_4^- \xrightarrow{heat} Ar{-}F + N_2 + BF_3$$

Example:



Aniline — Benzenediazonium chloride — Benzenediazonium fluoroborate — Fluorobenzene

Isolated as crystalline salt

(d) **Replacement by —OH. Discussed in Sec. 23.15.**

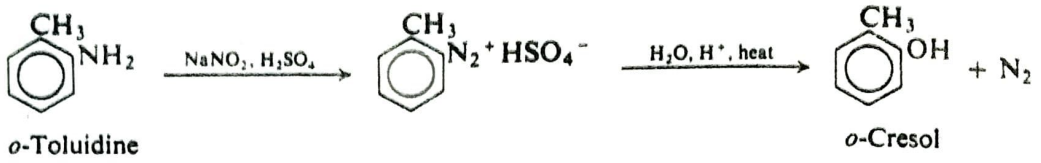
$$Ar{-}N_2^+ + H_2O \xrightarrow{H^+} Ar{-}OH + N_2$$

A phenol

CONTINUED

CONTINUED

Example:

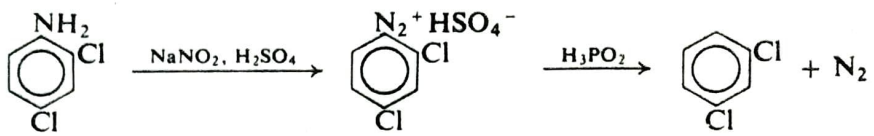


o-Toluidine *o*-Cresol

(e) Replacement by —H. Discussed in Sec. 23.16.

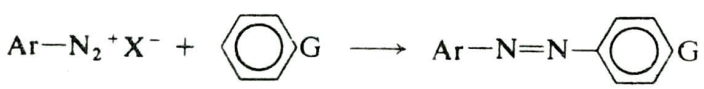
$$Ar{-}N_2^+ + H_3PO_2 \xrightarrow{H_2O} Ar{-}H + H_3PO_3 + N_2$$

Example:



2,4-Dichloroaniline *m*-Dichlorobenzene

2. Coupling. Discussed in Sec. 23.18.



An azo compound

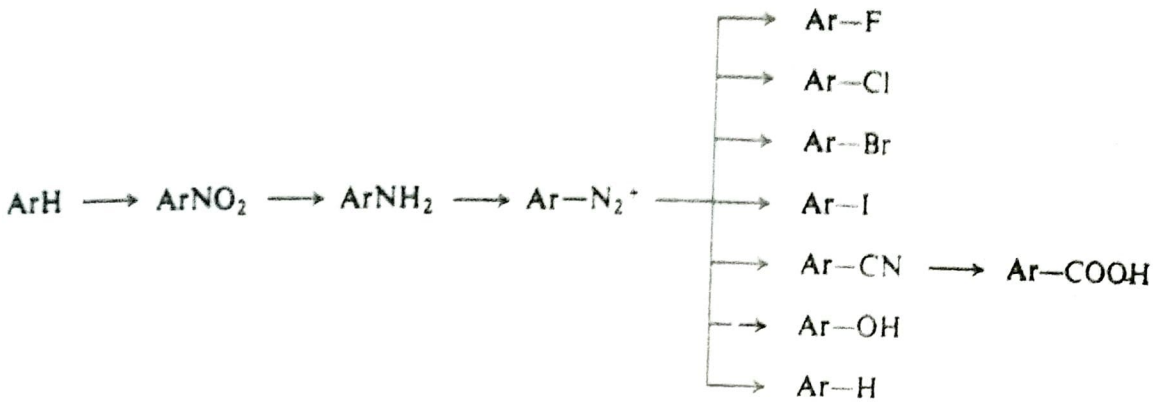
G must be a strongly electron-releasing group:
OH, NR_2, NHR, NH_2

Example:

Benzenediazonium chloride Phenol *p*-Hydroxyazobenzene
p-(Phenylazo)phenol ■

Replacement of the diazonium group is the best general way of introducing F, Cl, Br, I, CN, OH, and H into an aromatic ring. Diazonium salts are valuable in synthesis not only because they react to form so many classes of compounds, but also because they can be prepared from nearly all primary aromatic amines. There are few groups whose presence in the molecule interferes with diazotization; in this respect, diazonium salts are quite different from Grignard reagents (Sec. 18.18). The amines from which diazonium compounds are prepared are readily obtained from the corresponding nitro compounds, which are prepared by direct nitration. Diazonium salts are thus the most important link in the sequence shown below. In addition to the atoms and groups listed, there are dozens of other groups that can be attached to an aromatic ring by replacement of the diazonium nitrogen, as, for example, —Ar, $-NO_2$, —OR, —SH, —SR, —NCS, —NCO, $-PO_3H_2$, $-AsO_3H_2$, $-SbO_3H_2$; the best way to introduce most of these groups is via diazotization.

The coupling of diazonium salts with aromatic phenols and amines yields *azo compounds*, which are of tremendous importance to the dye industry.



23.13 Diazonium salts. Replacement by halogen. Sandmeyer reaction

Replacement of the diazonium group by —Cl or —Br is carried out by mixing the solution of freshly prepared diazonium salt with cuprous chloride or cuprous bromide. At room temperature, or occasionally at elevated temperatures, nitrogen is steadily evolved, and after several hours the aryl chloride or aryl bromide can be isolated from the reaction mixture. This procedure, using cuprous halides, is generally referred to as the **Sandmeyer reaction**.

$$Ar{-}N_2^+X^- \xrightarrow{CuX} Ar{-}X + N_2$$

Sometimes the synthesis is carried out by a modification known as the *Gattermann reaction*, in which copper powder and hydrogen halide are used in place of the cuprous halide.

Replacement of the diazonium group by —I does not require the use of a cuprous halide or copper; the diazonium salt and potassium iodide are simply mixed together and allowed to react.

$$Ar{-}N_2^+X^- + I^- \longrightarrow Ar{-}I + N_2 + X^-$$

Replacement of the diazonium group by —F is carried out in a somewhat different way. Addition of fluoroboric acid, HBF_4, to the solution of diazonium salt causes the precipitation of the diazonium fluoroborate, $ArN_2^+BF_4^-$, which can be collected on a filter, washed, and dried. The diazonium fluoroborates are unusual among diazonium salts in being fairly stable compounds. On being heated, the dry diazonium fluoroborate decomposes to yield the aryl fluoride, boron

$$Ar{-}N_2^+X^- \xrightarrow{HBF_4} Ar{-}N_2^+BF_4^- \xrightarrow{heat} Ar{-}F + BF_3 + N_2$$

trifluoride, and nitrogen. An analogous procedure involves the diazonium hexafluorophosphate, $ArN_2^+PF_6^-$.

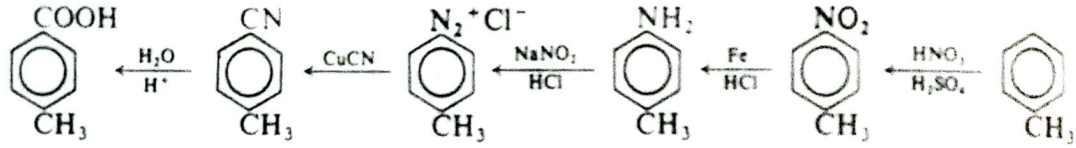
The advantages of the synthesis of aryl halides from diazonium salts will be discussed in detail in Sec. 26.3. Aryl fluorides and iodides cannot generally be prepared by direct halogenation. Aryl chlorides and bromides can be prepared by direct halogenation, but, when a mixture of *ortho* and *para* isomers is obtained, it is difficult to isolate the pure compounds because of their similarity in boiling point. Diazonium salts ultimately go back to nitro compounds, which are usually obtainable in pure form.

23.14 Diazonium salts. Replacement by —CN. Synthesis of carboxylic acids

Replacement of the diazonium group by —CN is carried out by allowing the diazonium salt to react with cuprous cyanide. To prevent loss of cyanide as HCN, the diazonium solution is neutralized with sodium carbonate before being mixed with the cuprous cyanide.

$$Ar{-}N_2^+X^- \xrightarrow{CuCN} Ar{-}CN + N_2$$

Hydrolysis of nitriles yields carboxylic acids. The synthesis of nitriles from diazonium salts thus provides us with an excellent route from nitro compounds to carboxylic acids. For example:



p-Toluic acid — *p*-Tolunitrile — *p*-Toluenediazonium chloride — *p*-Toluidine — *p*-Nitrotoluene — Toluene

This way of making aromatic carboxylic acids is more generally useful than either carbonation of a Grignard reagent or oxidation of side chains. We have just seen that pure bromo compounds, which are needed to prepare the Grignard reagent, are themselves most often prepared via diazonium salts; furthermore, there are many groups that interfere with the preparation and use of the Grignard reagent (Sec. 18.18). The nitro group can generally be introduced into a molecule more readily than an alkyl side chain; furthermore, conversion of a side chain into a carboxyl group cannot be carried out on molecules that contain other groups sensitive to oxidation.

23.15 Diazonium salts. Replacement by —OH. Synthesis of phenols

Diazonium salts react with water to yield phenols. This reaction takes place

$$Ar{-}N_2^+X^- + H_2O \longrightarrow Ar{-}OH + N_2 + H^+$$

slowly in the ice-cold solutions of diazonium salts, and is the reason diazonium salts are used immediately upon preparation; at elevated temperatures it can be made the chief reaction of diazonium salts.

As we shall see, phenols can couple with diazonium salts to form azo compounds (Sec. 23.18); the more acidic the solution, however, the more slowly this coupling occurs. To minimize coupling during the synthesis of a phenol, therefore—coupling, that is, between phenol that has been formed and diazonium ion that has not yet reacted—the diazonium solution is added slowly to a large volume of boiling dilute sulfuric acid.

This is the best general way to make the important class of compounds, the phenols.

23.16 Diazonium salts. Replacement by —H

Replacement of the diazonium group by —H can be brought about by a number of reducing agents; perhaps the most useful of these is *hypophosphorous acid*, H_3PO_2. The diazonium salt is simply allowed to stand in the presence of the hypophosphorous acid; nitrogen is lost, and hypophosphorous acid is oxidized to phosphorous acid:

$$Ar{-}N_2^+X^- + H_3PO_2 + H_2O \longrightarrow Ar{-}H + N_2 + H_3PO_3 + HX$$

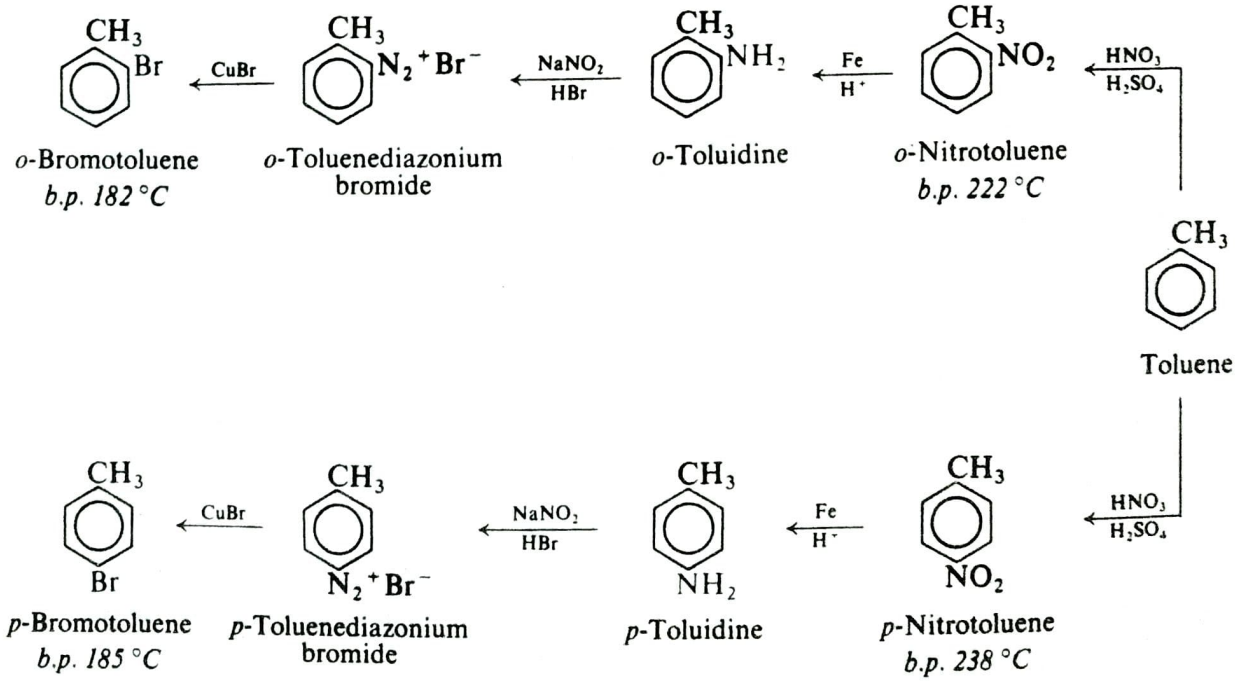
An especially elegant way of carrying out this replacement is to use hypophosphorous acid as the diazotizing acid. The amine is dissolved in hypophosphorous acid, and sodium nitrite is added; the diazonium salt is reduced as fast as it is formed.

This reaction of diazonium salts provides a method of removing an $-NH_2$ or $-NO_2$ group from an aromatic ring. This process can be extremely useful in synthesis, as is shown in some of the examples in the following section.

23.17 Syntheses using diazonium salts

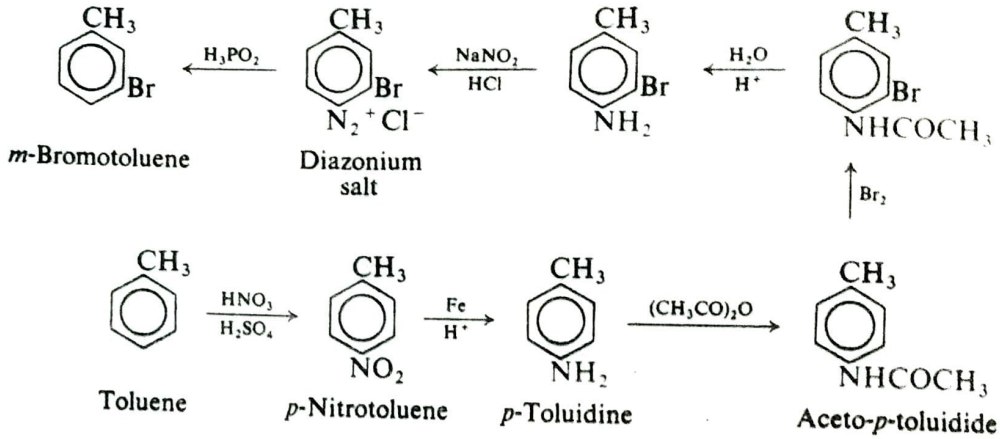
Let us look at a few examples of how diazonium salts can be used in organic synthesis.

To begin with, we might consider some rather simple compounds, the three isomeric bromotoluenes. The best synthesis of each employs diazotization, but not for the same purpose in the three cases. The *o*- and *p*-bromotoluenes are prepared from the corresponding *o*- and *p*-nitrotoluenes:



The advantage of these many-step syntheses over direct bromination is, as we have seen, that a pure product is obtained. Separation of the *o*- and *p*-bromotoluenes obtained by direct bromination is not feasible.

Synthesis of *m*-bromotoluene is a more complicated matter. The problem here is one of preparing a compound in which two *ortho,para*-directing groups are situated *meta* to each other. Bromination of toluene or methylation of bromobenzene would not yield the correct isomer. *m*-Bromotoluene is obtained by the following sequence of reactions:

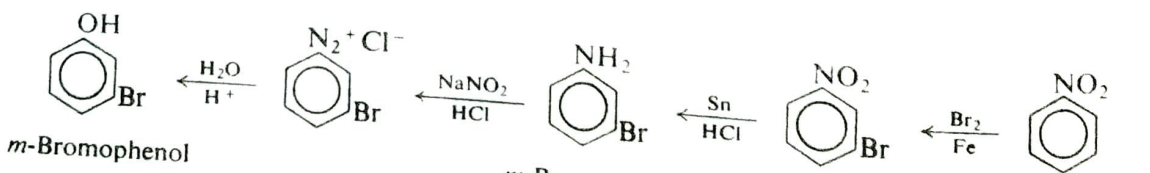


m-Bromotoluene — Diazonium salt — Toluene — *p*-Nitrotoluene — *p*-Toluidine — Aceto-*p*-toluidide

The key to the synthesis is the introduction of a group that is a much stronger *ortho,para* director than $-CH_3$, and that can be easily removed after it has done its job of directing bromine to the correct position. Such a group is the $-NHCOCH_3$ group: it is introduced into the *para* position of toluene via nitration, reduction, and acetylation; it is readily removed by hydrolysis, diazotization, and reduction.

Problem 23.12 Outline the synthesis from benzene or toluene of the following compounds: *m*-nitrotoluene, *m*-iodotoluene, 3,5-dibromotoluene, 1,3,5-tribromobenzene, the three toluic acids ($CH_3C_6H_4COOH$), the three methylphenols (cresols).

In the synthesis of *m*-bromotoluene, advantage was taken of the fact that the diazonium group is prepared from a group that is strongly *ortho,para*-directing. Ultimately, however, the diazonium group is prepared from the $-NO_2$ group, which is a strongly *meta*-directing group. Advantage can be taken of this fact, too, as in the preparation of *m*-bromophenol:

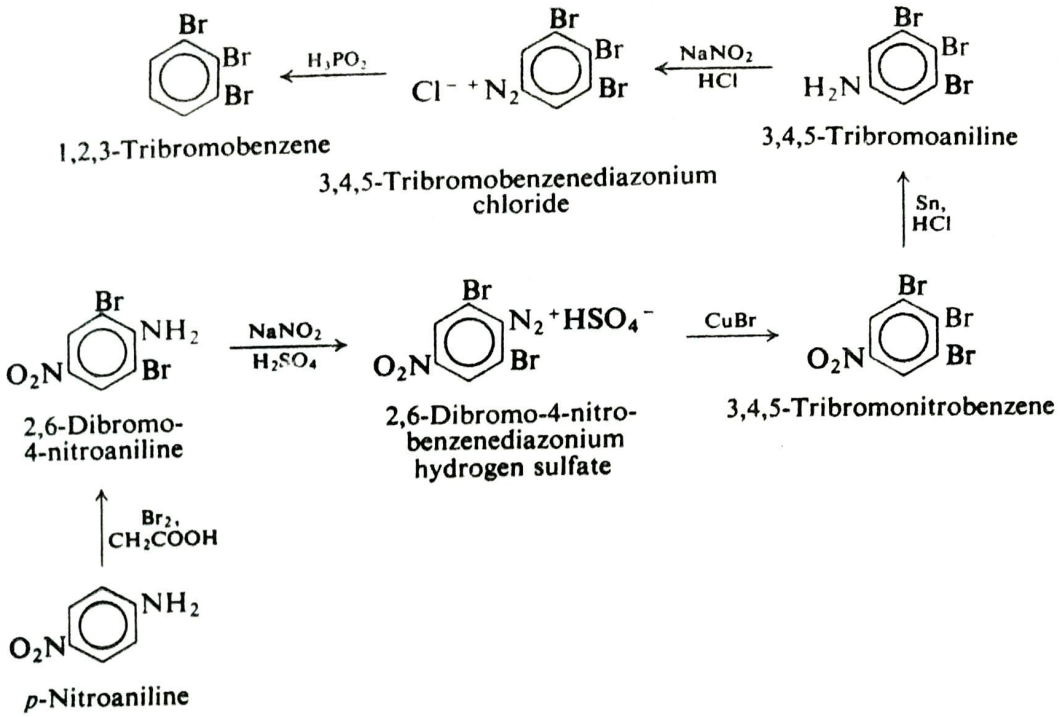


m-Bromophenol — *m*-Bromobenzenediazonium chloride — *m*-Bromoaniline — *m*-Bromonitrobenzene — Nitrobenzene

Here again there is the problem of preparing a compound with two *ortho,para* directors situated *meta* to each other. Bromination at the nitro stage gives the necessary *meta* orientation.

Problem 23.13 Outline the synthesis from benzene or toluene of the following compounds: *m*-dibromobenzene, *m*-bromoiodobenzene.

As a final example, let us consider the preparation of 1,2,3-tribromobenzene:



In this synthesis advantage is taken of the fact that the $-NO_2$ group is a *meta* director, that the $-NH_2$ group is an *ortho,para* director, and that each of them can be converted into a diazonium group. One diazonium group is replaced by —Br, the other by —H.

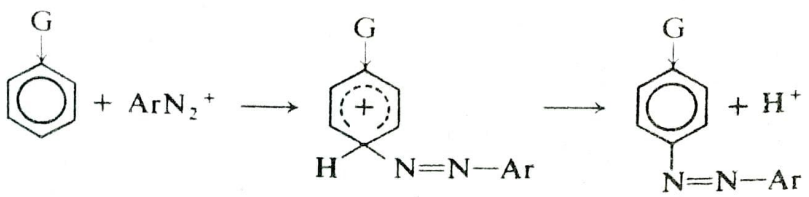
23.18 Coupling of diazonium salts. Synthesis of azo compounds

Under the proper conditions, diazonium salts react with certain aromatic compounds to yield products of the general formula Ar—N=N—Ar′, called **azo compounds.** In this reaction, known as **coupling**, the nitrogen of the diazonium group is retained in the product, in contrast to the replacement reactions we have studied up to this point, in which nitrogen is lost.

$$ArN_2^+ + Ar'H \longrightarrow \underset{\text{An azo compound}}{Ar{-}N{=}N{-}Ar'} + H^+$$

The aromatic ring (Ar′H) undergoing attack by the diazonium ion must, in general, contain a powerfully electron-releasing group, generally —OH, $-NR_2$, —NHR, or $-NH_2$. Substitution usually occurs *para* to the activating group. Typically, coupling with phenols is carried out in mildly alkaline solution, and with amines in mildly acidic solution.

Activation by electron-releasing groups, as well as the evidence of kinetics studies, indicates that coupling is electrophilic aromatic substitution in which the diazonium ion is the attacking reagent:



It is significant that the aromatic compounds which undergo coupling are also the ones which undergo nitrosation. Like the nitrosonium ion, ^+NO, the diazonium ion, ArN_2^+, is evidently very weakly electrophilic, and is capable of attacking only very reactive rings.

Problem 23.14 Benzenediazonium chloride couples with phenol, but not with the less reactive anisole. 2,4-Dinitrobenzenediazonium chloride, however, couples with anisole; 2,4,6-trinitrobenzenediazonium chloride even couples with the hydrocarbon mesitylene (1,3,5-trimethylbenzene). (a) How can you account for these differences in behavior? (b) Would you expect *p*-toluenediazonium chloride to be more or less reactive as a coupling reagent than benzenediazonium chloride?

In the laboratory we find that coupling involves more than merely mixing together a diazonium salt and a phenol or amine. Competing with any other reaction of diazonium salts is the reaction with water to yield a phenol. If coupling proceeds slowly because of unfavorable conditions, phenol formation may very well become the major reaction. Furthermore, the phenol formed from the diazonium salt can itself undergo coupling; even a relatively small amount of this undesired coupling product could contaminate the desired material—usually a dye whose color should be as pure as possible—to such an extent that the product would be worthless. Conditions under which coupling proceeds as rapidly as possible must therefore be selected.

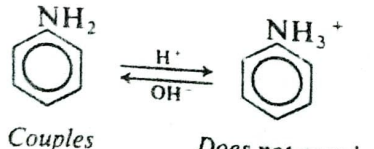
It is most important that the coupling medium be adjusted to the right degree of acidity or alkalinity. This is accomplished by addition of the proper amount of hydroxide or salts like sodium acetate or sodium carbonate. It will be well to examine this matter in some detail, since it illustrates a problem that is frequently encountered in organic chemical practice.

The electrophilic reagent is the diazonium ion, ArN_2^+. In the presence of hydroxide ion, the diazonium ion exists in equilibrium with an un-ionized compound, Ar—N=N—OH, and salts (Ar—N=N—O^-Na^+) derived from it:

$$\underset{\textit{Couples}}{Ar{-}N{\equiv}N^+OH^-} \underset{H^+}{\overset{NaOH}{\rightleftharpoons}} \underset{\textit{Does not couple}}{Ar{-}N{=}N{-}OH} \underset{H^+}{\overset{NaOH}{\rightleftharpoons}} \underset{\textit{Does not couple}}{Ar{-}N{=}N{-}O^-Na^+}$$

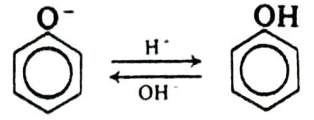
For our purpose we need only know that hydroxide tends to convert diazonium ion, which couples, into compounds which do not couple. In so far as the electrophilic reagent is concerned, then, coupling will be favored by a low concentration of hydroxide ion, that is, by high acidity.

But what is the effect of high acidity on the amine or phenol with which the diazonium salt is reacting? Acid converts an amine into its ion, which, because of the positive charge, is relatively unreactive toward electrophilic aromatic substitution: much too unreactive to be attacked by the weakly electrophilic diazonium ion. The higher the acidity, the higher the proportion of amine that exists as its ion, and the lower the rate of coupling.



Couples *Does not couple*

An analogous situation exists for a phenol. A phenol is appreciably acidic; in aqueous solutions it exists in equilibrium with phenoxide ion:



Couples rapidly *Couples slowly*

The fully developed negative charge makes —O^- much more powerfully electron-releasing than —OH; the phenoxide ion is therefore much more reactive than the un-ionized phenol toward electrophilic aromatic substitution. The higher the acidity of the medium, the higher the proportion of phenol that is un-ionized, and the lower the rate of coupling. In so far as the amine or phenol is concerned, then, coupling is favored by low acidity.

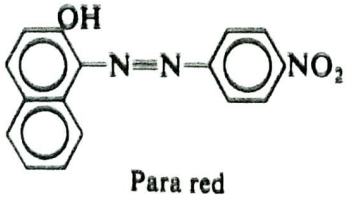
The conditions under which coupling proceeds most rapidly are the result of a compromise. The solution must not be so alkaline that the concentration of diazonium ion is too low; it must not be so acidic that the concentration of free amine or phenoxide or phenoxide ion is too low. It turns out that amines couple fastest in mildly acidic solutions, and phenols couple fastest in mildly alkaline solutions.

Problem 23.15 Suggest a reason for the use of *excess* mineral acid in the diazotization process.

Problem 23.16 (a) Coupling of diazonium salts with primary or secondary aromatic amines (but not with tertiary aromatic amines) is complicated by a side reaction that yields an isomer of the azo compound. Judging from the reaction of secondary aromatic amines with nitrous acid (Sec. 23.11), suggest a possible structure for this by-product.

(b) Upon treatment with mineral acid, this by-product regenerates the original reactants which recombine to form the azo compound. What do you think is the function of the acid in this regeneration? (*Hint*: See Sec. 8.26.)

Azo compounds are the first compounds we have encountered that as a class are strongly colored. They can be intensely yellow, orange, red, blue, or even green,



Para red
A red dye

Methyl orange
An acid–base indicator:
red in acid, *yellow* in base

depending upon the exact structure of the molecule. Because of their color, the azo compounds are of tremendous importance as dyes; about half of the dyes in industrial use today are azo dyes. Some of the acid–base indicators with which we are already familiar are azo compounds.

Problem 23.17 An azo compound is cleaved at the azo linkage by stannous chloride, $SnCl_2$, to form two amines. (a) What is the structure of the azo compound that is cleaved to 3-bromo-4-aminotoluene and 2-methyl-4-aminophenol? (b) Outline a synthesis of this azo compound, starting with benzene and toluene.

23.19 Analysis of amines. Hinsberg test

Amines are characterized chiefly through their basicity. A water-insoluble compound that dissolves in cold dilute hydrochloric acid—or a water-soluble compound (not a salt, Sec. 19.21) whose aqueous solution turns litmus blue—must almost certainly be an amine (Secs. 22.5 and 23.2). Elemental analysis shows the presence of nitrogen.

Whether an amine is primary, secondary, or tertiary is best shown by the **Hinsberg test**. The amine is shaken with benzenesulfonyl chloride in the presence of aqueous *potassium* hydroxide (Sec. 23.7). Primary and secondary amines form substituted sulfonamides; tertiary amines do not—*if* the test is carried out properly.

The monosubstituted sulfonamide from a primary amine has an acidic hydrogen attached to nitrogen. Reaction with potassium hydroxide converts this amide into a soluble salt which, *if the amine contained fewer than eight carbons*, is at least partly soluble. Acidification of this solution regenerates the insoluble amide.

The disubstituted sulfonamide from a secondary amine has no acidic hydrogen and remains insoluble in the alkaline reaction mixture.

Now, the all-important question: what do we actually observe when we treat an amine with benzenesulfonyl chloride and excess potassium hydroxide? A *primary amine* yields a clear solution, from which, upon acidification, an insoluble material separates. A *secondary amine* yields an insoluble compound, which is unaffected by acid. A *tertiary amine* yields an insoluble compound (the unreacted amine itself) which dissolves upon acidification of the mixture.

$$\underset{\text{1° amine}}{RNH_2} + C_6H_5SO_2Cl \xrightarrow{OH^-} [C_6H_5SO_2NHR] \xrightarrow{KOH} \underset{\textit{Clear solution}}{C_6H_5SO_2NR^-K^+} \xrightarrow{H^+} \underset{\textit{Insoluble}}{C_6H_5SO_2NHR}$$

$$\underset{\text{2° amine}}{R_2NH} + C_6H_5SO_2Cl \xrightarrow{OH^-} \underset{\textit{Insoluble}}{C_6H_5SO_2NR_2} \xrightarrow{KOH \text{ or } H^+} \text{No reaction}$$

$$\underset{\text{3° amine}}{R_3N} + C_6H_5SO_2Cl \xrightarrow{OH^-} \underset{\textit{Insoluble}}{R_3N} \xrightarrow{HCl} \underset{\textit{Clear solution}}{R_3NH^+Cl^-}$$

Like all experiments, the Hinsberg test must be done *carefully* and interpreted *thoughtfully*. Among other things, misleading side reactions can occur if the proportions of reagents are incorrect, or if the temperature is too high or the time of reaction too long. Tertiary amines evidently *react*—after all, they are just as nucleophilic as other amines; but the initial product (I) has no acidic proton to

$$C_6H_5SO_2Cl + R_3N \longrightarrow \underset{\text{I}}{C_6H_5SO_2NR_3^+Cl^-} \xrightarrow{OH^-} C_6H_5SO_3^- + R_3N + Cl^-$$

lose, and ordinarily is hydrolyzed to regenerate the amine.

Behavior toward nitrous acid (Sec. 23.11) is of some use in determining the class of an amine. In particular, the behavior of primary aromatic amines is quite characteristic: treatment with nitrous acid converts them into diazonium salts, which yield highly colored azo compounds upon treatment with β-naphthol (a phenol, see Sec. 23.18).

Among the numerous derivatives useful in identifying amines are: amides (e.g., acetamides, benzamides, or sulfonamides) for primary and secondary amines; quaternary ammonium salts (e.g., those from benzyl chloride or methyl iodide) for tertiary amines.

Problem 23.18 In non-aqueous medium, the product $C_6H_5SO_2N(CH_3)_3^+Cl^-$ can actually be isolated from the reaction of benzenesulfonyl chloride with one equivalent of trimethylamine. When *two* equivalents of the amine are used, there is formed, slowly, $C_6H_5SO_2N(CH_3)_2$ and $(CH_3)_4N^+Cl^-$. (a) Give all steps in a likely mechanism for the latter reaction. What fundamental type of reaction is probably involved?

(b) If, in carrying out the Hinsberg test, the reaction mixture is heated or allowed to stand, many tertiary amines give precipitates. What are these precipitates likely to be? What incorrect conclusion about the unknown amine are you likely to draw?

Problem 23.19 The sulfonamides of big primary amines are only partially soluble in aqueous KOH. (a) In the Hinsberg test, what incorrect conclusion might you draw about such an amine? (b) How might you modify the procedure to avoid this mistake?

23.20 Analysis of substituted amides

A substituted amide of a carboxylic acid is characterized by the presence of nitrogen, insolubility in dilute acid and dilute base, and hydrolysis to a carboxylic acid and an amine. It is generally identified through identification of its hydrolysis products (Secs. 19.21 and 23.19).

23.21 Spectroscopic analysis of amines and substituted amides

Infrared The number and positions of absorption bands depend on the class to which the amine belongs (see Fig. 23.4, p. 878).

An amide, substituted or unsubstituted, shows the C=O band in the 1640–1690 cm^{-1} region. In addition, if it contains a free N—H group, it will show N—H stretching at 3050–3550 cm^{-1}, and —NH bending at 1600–1640 cm^{-1} ($RCONH_2$) or 1530–1570 cm^{-1} (RCONHR').

N—H stretching 3200–3500 cm^{-1}

1° Amines	2° Amines	3° Amines
Often two bands	*One band*	*No band*

N—H bending

1° Amines Strong bands 650–900 cm^{-1} (*broad*) and 1560–1650 cm^{-1}

C—N stretching

Aliphatic 1030–1230 cm^{-1} (*weak*) (3°: *usually a doublet*)

Aromatic 1180–1360 cm^{-1} (*strong*) *Two bands*

NMR Absorption by N—H protons of amines falls in the range δ 1–5, where it is often detected only by proton counting. Absorption by —CO—NH— protons of amides (Sec. 20.25) appears as a broad, low hump farther downfield (δ 5–8).

CMR The nitrogen of amines deshields carbon, and shifts absorption downfield.